A.M.A.
American Journal of DISEASES OF CHILDREN

SEPTEMBER 1955
VOLUME 90 NUMBER 3

INSENSIBLE WATER LOSSES PER DAY BY HOSPITALIZED INFANTS AND CHILDREN
ANN M. HEELEY, R.N., ET AL.

CASE FINDING IN RHEUMATIC FEVER
HELEN M. WALLACE, M.D., ET AL.

THROMBOCYTOPENIA AND GIANT HEMANGIOMA IN INFANTS
THOMAS A. GOOD, M.D., ET AL.

SALMONELLA SP. (TYPE MONTEVIDEO) OSTEOMYELITIS
N .C. ELLENBOGEN, M.D., ET AL.

TREATMENT OF STREPTOCOCCAL CARRIER STATE IN A RURAL SCHOOL
THOMAS B. HILL, M.D.

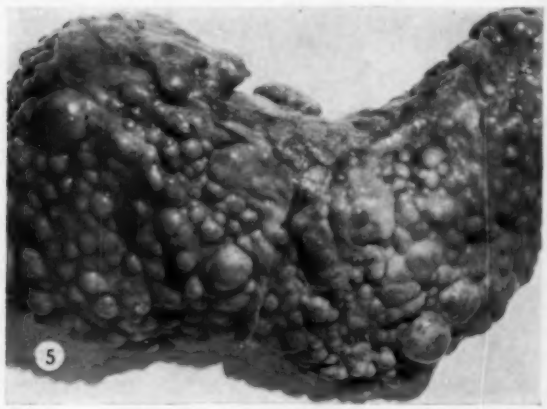
THE EPIDEMIOLOGICAL RETREAT OF TUBERCULOSIS
KARL E. KASSOWITZ, M.D.

EFFECT IN THE NEWBORN INFANT OF RESERPINE ADMINISTERED ANTE PARTUM
IRWIN S. BUDNICK, M.D., ET AL.

PORTAL HYPERTENSION IN INFANTS AND CHILDREN
DAVID YI-YUNG HSIA, M.D., ET AL.

COMPLETE CONTENTS ON FIRST PAGE

From Craig et al., p. 299



AMERICAN MEDICAL ASSOCIATION Publication

for strong, sturdy, solid growth

Lactum

LIQUID OR POWDERED

NUTRITIONALLY SOUND FORMULA FOR INFANTS

Lactum®-fed babies get all the proved benefits of a cow's milk and Dextri-Maltose® formula. Mothers appreciate the convenience and simplicity of this ready-prepared formula. Physicians are assured the important protein margin of safety for sturdy growth.

Lactum-fed babies are typically sturdy babies because Lactum supplies ample protein for sound growth and development.

The generous protein intake of babies fed milk and carbohydrate formulas such as Lactum promotes the formation of muscle mass. It also provides for good tissue turgor and excellent motor development.[1]

(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

MEAD

SYMBOL OF SERVICE TO THE PHYSICIAN

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U. S. A.

TABLE OF CONTENTS

VOLUME 90 SEPTEMBER 1955 NUMBER 3

ORIGINAL ARTICLES

PAGE

Insensible Water Losses per Day by Hospitalized Infants and Children
Ann M. Heeley, R.N., and Nathan B. Talbot, M.D., Boston 251

Case Finding in Rheumatic Fever
Helen M. Wallace, M.D.; Leah Hoenig, R.N., and Herbert Rich, New York 256

Thrombocytopenia and Giant Hemangioma in Infants
Thomas A. Good, M.D.; S. F. Carnazzo, M.D., and Robert A. Good, Ph.D., M.D., Minneapolis 260

Salmonella sp. (Type Montevideo) Osteomyelitis
N. C. Ellenbogen, M.D.; Jerome Raim, M.D., and L. Grossman, M.D., Miami, Fla. 275

Treatment of Streptococcal Carrier State in a Rural School
Thomas B. Hill, M.D., Lowell, Mich. 280

The Epidemiological Retreat of Tuberculosis
Karl E. Kassowitz, M.D., Milwaukee 283

Effect in the Newborn Infant of Reserpine Administered ante Partum
Irwin S. Budnick, M.D.; Sanford Leikin, M.D., and Leroy E. Hoeck, M.D., Washington, D. C. 286

Portal Hypertension in Infants and Children
David Yi-Yung Hsia, M.D., and Sydney S. Gellis, M.D., Boston 290

PROGRESS IN PEDIATRICS

Cirrhosis of the Liver in Infants and Children
John M. Craig, M.D.; Sydney S. Gellis, M.D., and David Yi-Yung Hsia, M.D., Boston 299

Acute Nonlipid Disseminated Reticuloendotheliosis
Randolph Batson, M.D.; John Shapiro, M.D.; Amos Christie, M.D., and H. D. Riley Jr., M.D., Nashville, Tenn. 323

Vitamin B_6 Deficiency in Infants
David Baird Coursin, M.D., Lancaster, Pa. 344

CASE REPORTS

Thrombocytopenic Purpura Occurring with Large Hemangioma
Capt. Edwin A. Meeks (MC), U. S. Army; Major Jack B. Jay (MC), U. S. Air Force, and Major Gen. Leonard D. Heaton (MC), U. S. Army 349

REGULAR DEPARTMENTS

Abstracts from Current Literature 352

News and Comment 279, 282

Books 371

A. M. A.
American Journal of Diseases of Children

VOLUME 90 SEPTEMBER 1955 NUMBER 3

COPYRIGHT, 1955, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

ROBERT BARRETT LAWSON, Chief Editor
1000 N. W. 17th St., Miami 36, Fla.

A. A. WEECH, Cincinnati
ROGER L. J. KENNEDY, Rochester, Minn.
FRANCIS SCOTT SMYTH, San Francisco
JAMES L. WILSON, Ann Arbor, Mich.
ROBERT A. ALDRICH, Portland, Ore.
RICHARD L. DAY, Brooklyn
WARREN E. WHEELER, Columbus, Ohio
WOLF W. ZUELZER, Detroit

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION
Scientific Publications

The Journal of the American Medical Association. Weekly. Annual Subscription Price, $15.00.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $20.00.

A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

A. M. A. Archives of Dermatology. Herbert Rattner, M.D., Chief Editor, 104 S. Michigan Ave., Chicago. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.

A. M. A. American Journal of Diseases of Children. Robert B. Lawson, M.D., Chief Editor, 1000 N.W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $8.00; Canada, $8.50; Foreign, $9.25; individual copy, $1.00.

A. M. A. Archives of Neurology and Psychiatry. Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $8.00; Canada, $8.50; Foreign, $9.00; individual copy, $1.00.

Check, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

VARAMEL
MEL®
Made from Grade A Cow's Milk
A formula base made from Grade A cow's milk (U. S. Public Health Service Milk Code) in which the milk fat has been replaced by coconut oil, destearinated beef fat, and corn oil, with the addition of vitamin A palmitate, activated 7-dehydrocholesterol, ascorbic acid, thiamine, niacinamide, and iron ammonium citrate.

The first in infant feeding

to be made exclusively from grade A milk*

This statement is your assurance of the use of high quality, clean milk. Make a habit of looking for it on the label of products which you prescribe for infant feeding.

We firmly believe that the quality of the ingredients is reflected in the quality of the final product!

*U. S. Public Health Service Milk Code

THE BAKER LABORATORIES, INC.

Milk Products Exclusively for the Medical Profession

MAIN OFFICE: CLEVELAND 3, OHIO PLANT: EAST TROY, WISCONSIN

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript and the first carbon of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

Typographic considerations necessitate that the first paragraph of an article contain not fewer than thirty words. A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted. If such material is quoted indirectly, the author must be careful to leave no complete sentence of the original unaltered. Use of uncredited quotations will be sufficient cause for rejection of an article.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. Submit sharp prints of the following sizes, 2½″ wide × 2½″ or 3½″ high, 3½″ wide × 2½″ high, and 5½″ or 7″ wide × 3½″ high, to minimize reduction and/or cropping. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins or mountings rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. IT IS PREFERRED THAT ILLUSTRATIONS BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

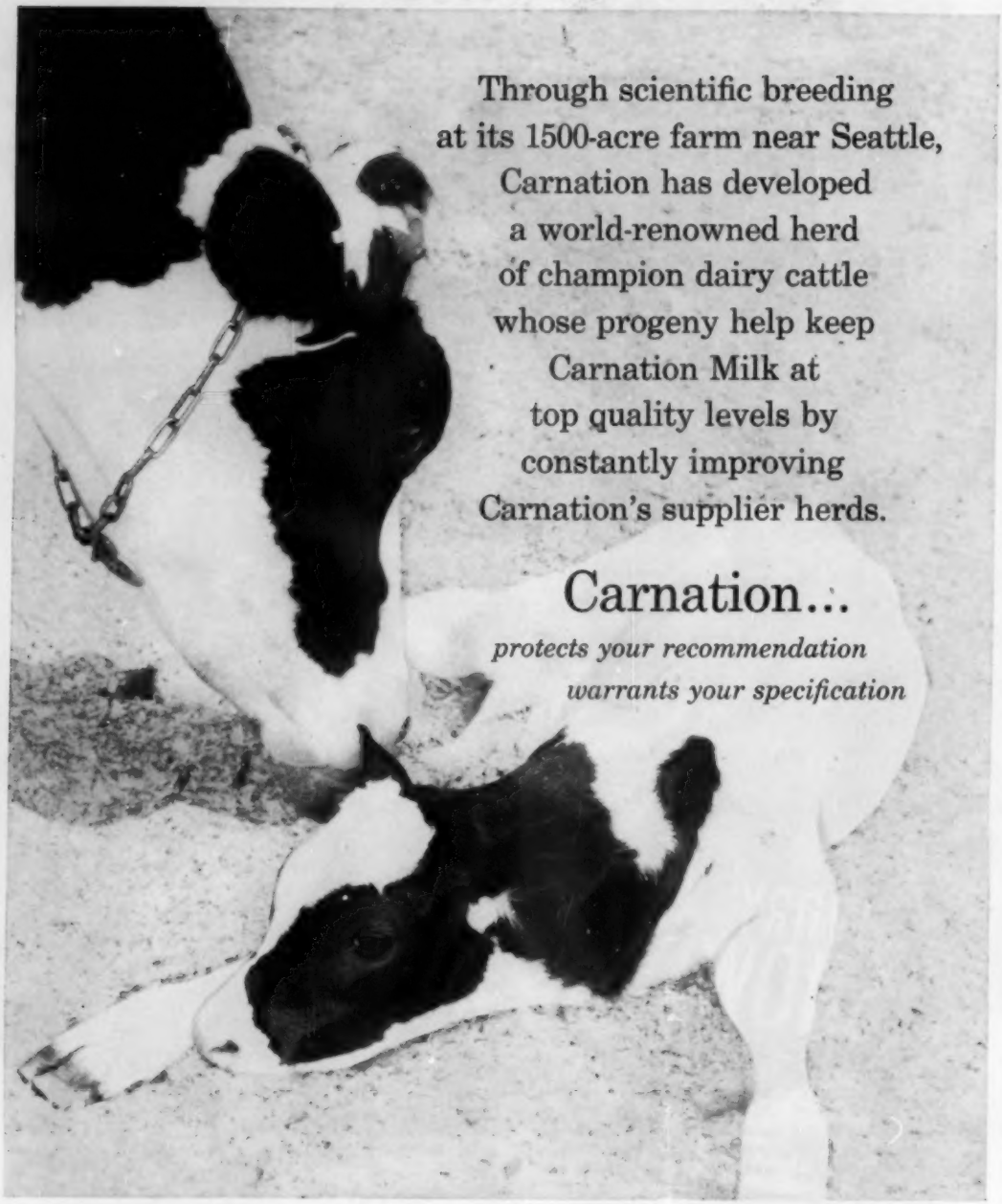
IVORY SNOW

Safe and mild as a soap can be for diapers and baby things.

No other washing product leaves diapers and baby clothes softer...and they're free of irritating deposits that chafe baby's tender skin.

IVORY SNOW IS IVORY-SAFE . . . "99⁴⁴/₁₀₀% PURE®".

A Procter & Gamble Product



Doctor, may we have your support for

They're ALL Instant!

Instant S-M-A Powder means *instant* convenience for busy mothers . . . just as it means dependable nutrition for their babies.

It's 1, 2, 3, 4—empty, measure, shake, and pour. That's all there is to it.

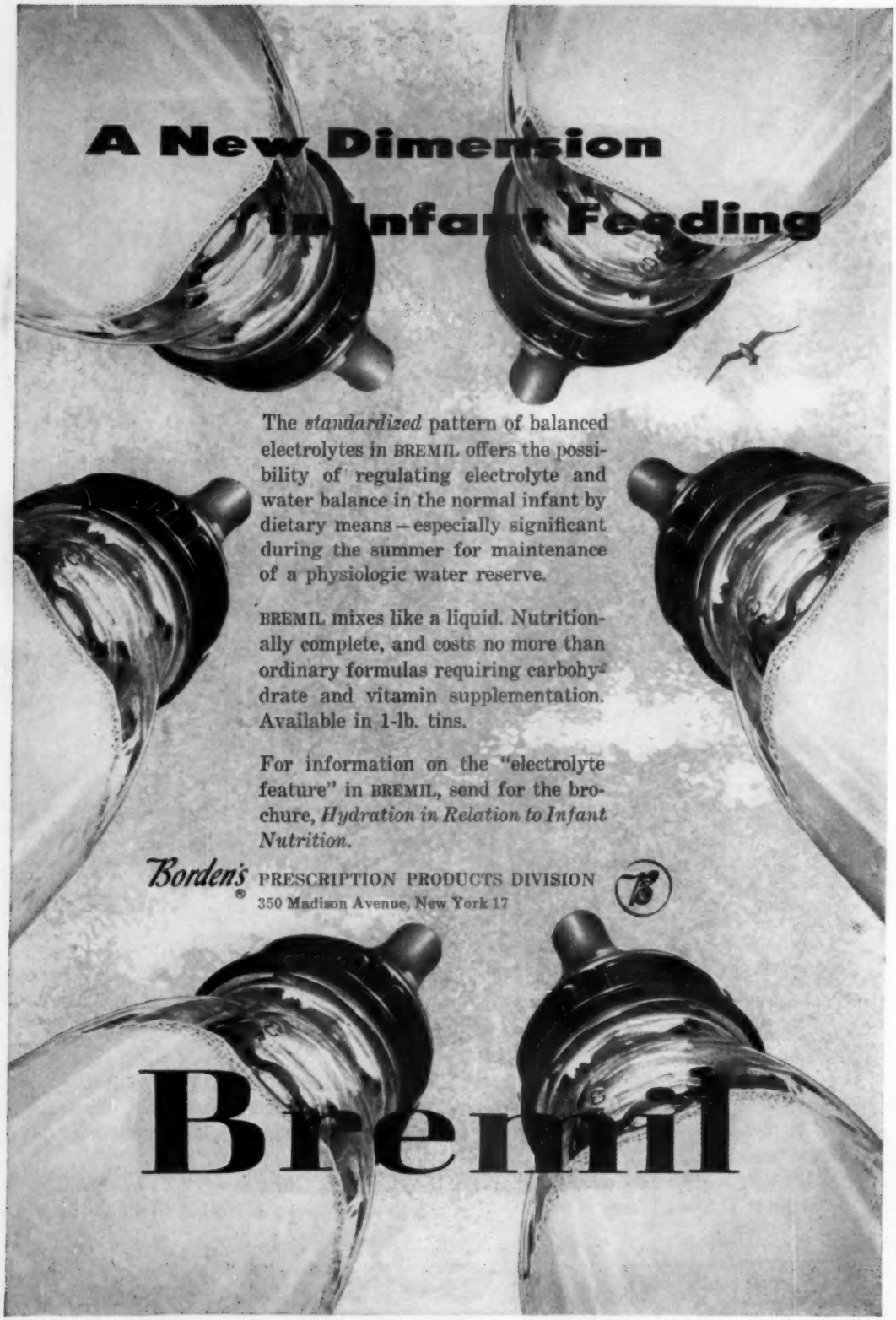
And Instant S-M-A Powder is the same distinguished formula that physicians everywhere have long prescribed.

Supplied: Glass jars of 3.54 oz. Each jar makes 26 oz. of S-M-A formula.

Wyeth®
Philadelphia 2, Pa.

INSTANT **S-M-A**® POWDER

Modern Infant Formula


A New Dimension
in Infant Feeding
The *standardized* pattern of balanced electrolytes in BREMIL offers the possibility of regulating electrolyte and water balance in the normal infant by dietary means—especially significant during the summer for maintenance of a physiologic water reserve.
BREMIL mixes like a liquid. Nutritionally complete, and costs no more than ordinary formulas requiring carbohydrate and vitamin supplementation. Available in 1-lb. tins.
For information on the "electrolyte feature" in BREMIL, send for the brochure, *Hydration in Relation to Infant Nutrition.*
Borden's
PRESCRIPTION PRODUCTS DIVISION
350 Madison Avenue, New York 17
Bremil

How flexible is a Selby shoe?

Some shoes for children are made of stiff, hard leathers. Others are made almost entirely of soft, flexible leathers. The ideal shoe for a child requires a careful combination of firm and flexible leathers. Selby Junior Arch Preserver Shoes have insoles of sturdy, extra heavy weight leathers to eliminate ridges and curling. The upper leathers are light, strong, long-wearing, with a fine flexibility in the forepart of the shoes. Selby Juniors are flexible in that part of the shoe where flexibility is most desirable, without the sacrifice of extra heavy leathers in those areas of the shoe where such leathers are required. The excellence of Selby Junior Arch Preservers is the result of the knowledge and skill required in more than three quarters of a century of fine shoemaking. When you recommend shoes for infants and children, please remember—Selby Juniors are the only *genuine* Arch Preserver Shoes for children.

BROAD BASED HEEL

WEDGE CONSTRUCTION

ALLOY SPRING STEEL SHANK

The only genuine Arch Preserver Shoes for children

• *If Selby Junior Arch Preservers are not available in your city, please write directly to us.*

The Selby Shoe Company
Portsmouth, Ohio

Selby JUNIOR ARCH PRESERVER Shoes

MORE THAN THREE QUARTERS OF A CENTURY OF FINE SHOEMAKING

to reduce complications
in the first year of life

SIMILAC®

a source of nutritional protection against infantile eczema...

▪ Linoleic and other unsaturated fatty acids believed to play an important role in the prevention and therapy of infantile eczema[1-4] are present in Similac, in amounts at least equal to those reported for breast milk.[5]

▪ Similac, in recommended quantities, provides protein closely approximating the physiologic level supplied by breast milk.[6] The fluidity of Similac protein, comparable to that of breast milk protein, assures rapid and complete digestion.[7] There is thus virtually no likelihood that products of incomplete digestion will be absorbed to cause an allergic eczematous reaction. In contrast, customary cow's milk mixtures are believed to deliver excessive amounts of protein, some of which cannot be completely digested and may be absorbed to cause a vascular reaction in the upper corium.[8]

there is no closer equivalent to the milk of healthy, well-nourished mothers

SUPPLIED: as Powder in tins of 1 lb., with measuring cup; as Liquid in tins of 13 fl. oz.

1. Editorial: J.A.M.A. *134*:606 (June 14) 1947. 2. Hansen, A. E., and Burr, G. O.: J.A.M.A. *132*:855 (Dec. 7) 1946. 3. Hansen, A. E.; Knott, E. M.; Wiese, H. F.; Shaperman, E., and McQuarrie, I.: Am. J. Dis. Child. *73*:1 (Jan.) 1947. 4. Hansen, A. E.: In, Vitamin B_6 in Human Nutrition, Report of the Tenth M & R Pediatric Research Conference, Columbus, M & R Laboratories, 1954, p. 51. 5. National Research Council: Maternal Nutrition and Child Health, Bull. 123 (Nov.) 1950. 6. Meyer, H. F.: Essentials of Infant Feeding for Physicians, Springfield, Illinois, Charles C. Thomas, 1952, p. 44. 7. Martin, C. W.: New York State J. Med. *32*:1012 (Sept.) 1932. 8. Stoesser, A. V., and Nelson, L. S.: Journal Lancet *73*:487 (Dec.) 1953.

M & R LABORATORIES, *Columbus 16, Ohio*

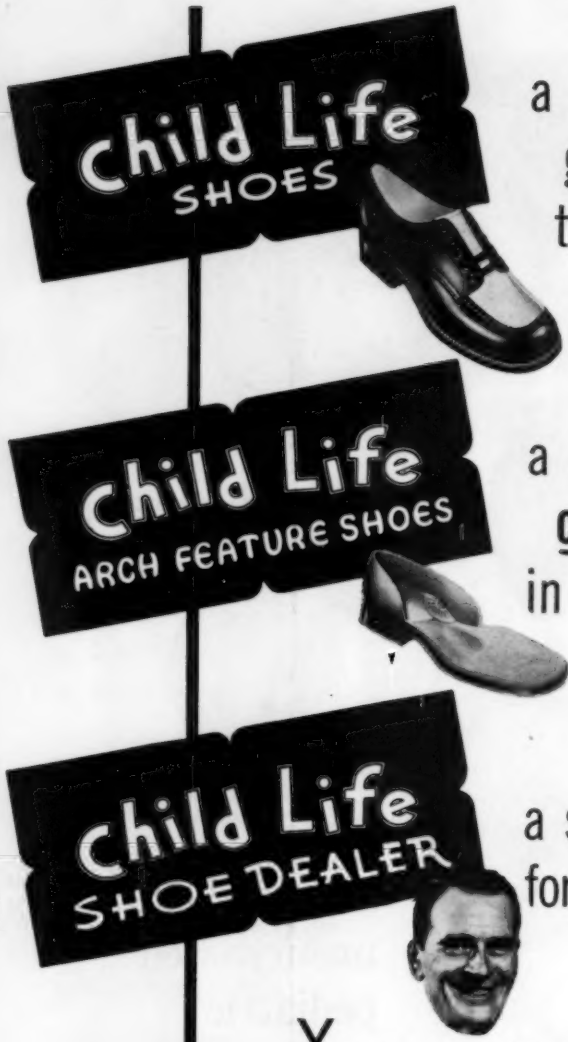
an
unsurpassed
pediatric
antihistamine

Pyribenzamine® Elixir

A palatable, spice-flavored antihistamine, Pyribenzamine Elixir offers highly effective therapy in a broad range of allergies. *Dosage can be readily adjusted* to any age, any individual requirement. *Prescribe this well-accepted medication* alone or as a therapeutic vehicle. Each 4-ml. teaspoonful contains 30 mg. Pyribenzamine citrate.

Pyribenzamine® citrate (tripelennamine citrate CIBA)

CIBA
SUMMIT, N. J.



a name that signifies
good construction
to the pediatrician

a name that stands for
corrective measures
in the care of pronation

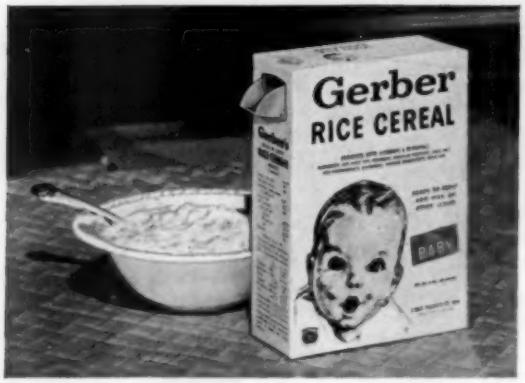
a symbol of **good service**
for every requirement of the
practitioner

You who work with children will find much of interest, and that you'll like, in CHILD LIFE Shoes — a juvenile line, now in its 30th year, that has built a reputation as a physician builds his — by performance.

CHILD LIFE Shoes are constructed to standards that encourage the development of normal foot growth . . . and they are crafted from the best of leathers by the most enduring of methods. CHILD LIFE Arch Feature Shoes have special built-in features that help you correct pronation — but their appearance is the same as "regular" CHILD LIFE Shoes. You'll like that.

And you'll like the CHILD LIFE dealer in your community. He has been hand-picked for his ethical standards, and you'll find him a good source for conscientious service. He will be most happy to call and show you all that CHILD LIFE Shoes provide. You'll do well to become acquainted — so please write and we'll have the nearest dealer contact you at once.

HERBST SHOE MANUFACTURING COMPANY
Milwaukee 45, Wisconsin



"Preferred Starting Subject"

Gerber Rice Cereal

Hypo-allergenic! Ideal starting solid for all babies, Gerber Rice Cereal is preferred where there is a family history of allergy. Prepared only from rice and hypo-allergenic nutritional supplements. Contains no yeast, malt or milk solids.

hypo-allergenic

Enriched! Gerber Rice Cereal is fortified with rice polishings — a particularly rich source of natural vitamin-B complex — plus crystalline thiamine, riboflavin and niacinamide. Iron is also added to support hemoglobin levels a few weeks after birth.

rich source of natural vitamin-B complex

Digestible! Thorough precooking and low crude fiber (averages 0.8%) assure easy digestibility. Bland flavor and smooth texture make Gerber Rice Cereal especially palatable to the young infant.

easy digestibility

Important P. S. Gerber Cereal Quads — a 4 in 1 assortment of Rice, Barley, Oatmeal and Cereal Food (a mixed cereal) — makes it easy and economical for the mother to introduce cereal variety. Once the baby is established on Rice, the other cereals may be introduced, one at a time. If cereal allergy shows up, diagnosis is relatively simple.

Gerber® BABY FOODS

FREMONT, MICHIGAN

4 CEREALS • OVER 65 STRAINED AND JUNIOR FOODS, INCLUDING MEATS

Babies are our business ... our only business!

One way to avoid sensitization to milk

PET Evaporated Milk really helps in the management of potentially allergic infants . . . because heat sterilization of Pet Milk coagulates whey proteins so they are less likely to be absorbed undigested into the blood stream. Instead, they are retained in the gastro-intestinal tract until digestion is complete. Recommend nutritious Pet Milk for *all* the babies in your care—it's good insurance against many feeding difficulties arising from milk sensitization.

Favored Form of Milk
For Infant Formula

PET MILK COMPANY, ARCADE BUILDING, ST. LOUIS 1, MO.

A.M.A. American Journal OF DISEASES of CHILDREN

Insensible Water Losses per Day by Hospitalized Infants and Children

ANN M. HEELEY, R.N.
and
NATHAN B. TALBOT, M.D., Boston

Water lost insensibly by way of the lungs and skin is an important factor in determining both the body requirement and the body tolerance for water.[1] Under conditions where homeostatic capacity to vary urine water output is greatly reduced by renal failure, insensible water loss (I. W. L.) may be the chief determinant of water tolerance.* A survey of the literature for information concerning I. W. L. by persons of various ages reveals that most observers have been interested primarily in relations between I. W. L. and energy output under basal conditions.[4] Very little information is available concerning the 24-hour losses of water occurring insensibly under the nonbasal conditions ordinarily pertaining in patients requiring parenteral fluid therapy or regulation of water intake because of pathologic oliguria or anuria.

Submitted for publication March 19, 1955.

From the Department of Pediatrics, Harvard Medical School and the Children's Medical Service, Massachusetts General Hospital, Boston.

This work was supported by a grant from the Commonwealth Fund of New York and aided in part by Grant H-1529 of the National Heart Institute, Public Health Service, and by a grant from Mead Johnson & Company.

* References 2 and 3.

It therefore appeared desirable to make a study of I. W. L. as it occurs over 24-hour periods under ordinary conditions of hospitalization. The present paper reports on 596 such measurements carried out during 45 periods of study on a total of 39 patients ranging in age from 2 months to 23 years.

CLINICAL MATERIAL AND METHODS

The Table gives the information concerning the subjects selected for study. All studies were carried out in the metabolic unit of the Children's Medical Service. With two exceptions, all observations were carried out between Oct. 1 and May 1 of each year. In the case of the two exceptions, some observations were made during the first two weeks of June. The temperature of the room air, which was recorded bidaily at 5 a. m. and 5 p. m., varied from 72 to 78 F, with a mean of 76 F. All patients wore light weight cotton or woolen clothing or had sufficient bed clothing to provide comfort. No visible perspiration was observed.

Each patient was under the constant supervision of graduate nurses working exclusively in the metabolic unit. Nude weights were obtained at the beginning and end of the study periods on a platform scale which was standardized daily and which had an accuracy of ±10 gm. Dietary and medicinal intake was weighed out with an accuracy of at least 1 gm. Intravenous fluid intake was measured on a standard burette graduated in 5 ml. increments, with all fluids infused assumed to weigh 1 gm/ml. Urinary output was measured in glass cylinders graduated in 5 ml. increments after collection in stainless steel bedpans which were washed and dried between voidings. The total volume in milliliters was converted to weight in grams by means of specific gravity determinations. Stool output was

Observed Values for Age, Height, Weight, and Insensible Water Loss *

Patient	Sex	Age, Yr.	Height, Cm.	Weight, Kg.	Surface Area, Sq. M.	Days of Observation	Average Insensible Water Loss, Ml/24 Hr.	Diagnosis and Comment
1	M	2/12	58	5.1	0.26	5	260	Postoperative cystic hygroma of neck
2	M	4/12	58	5.4	0.30	2	305	Diarrhea with dehydration under parenteral fluid therapy
3	M	4/12	59	4.9	0.28	7	313	Milk allergy
4	M	11/12	80	10.0	0.48	2	810	Diarrhea with dehydration under parenteral fluid therapy
5	M	1 1/12	82	12.5	0.51	2	465	Diarrhea with dehydration under parenteral fluid therapy
6	M	2 3/12	88	17.0	0.61	40	425	Nephrosis, estimated normal weight, 13.0 kg.
7 (*a*)	F	2 4/12	61	5.6	0.29	2	381	Idiopathic dwarfism
(*b*)	..	4 6/12	70	7.3	0.36	23	375	
8	M	2 6/12	81	12.9	0.52	2	701	Stunted growth; active child
9	F	2 10/12	84	12.2	0.50	4	465	Renal rickets; physical deformities limited activity
10	M	3 4/12	97	14.4	0.60	6	669	Osteogenesis imperfecta
11	F	3 8/12	116	20.3	0.78	4	715	Acute glomerulonephritis; bedrest with sedation
12	M	3 9/12	103	25.0	0.83	8	526	Nephrosis; estimated normal weight, 17.0 kg.
13	F	3 11/12	103	16.6	0.68	4	920	Moniliasis of mouth and scalp
14	M	4 2/12	89	8.7	0.46	17	541	Dwarfism due to caloric undernutrition
15	M	4 5/12	107	22.0	0.77	33	590	Nephrosis; estimated normal weight, 19.0 kg.
16	F	4 5/12	102	16.5	0.67	4	383	Convulsions; congenital hemiplegia; very inactive
17 (*a*)	F	5 2/12	111	20.0	0.75	24	766	Nephrosis; estimated normal weight, 19.0 kg.
(*b*)	..	5 11/12	116	26.0	0.88	28	636	Estimated normal weight, 21.0 kg.
(*c*)	..	7 8/12	129	37.3	1.22	2	848	Estimated normal weight, 27.0 kg.
18	M	5 5/12	106	17.5	0.72	4	488	Chronic pannephritis; estimated normal weight, 16.0 kg.
19	F	5 5/12	112	20.0	0.80	3	648	Appendectomy
20	M	6 3/12	111	19.4	0.77	17	539	Chronic glomerulonephritis, inactive
21	M	6 4/12	110	31.0	0.70	28	811	Asthma, asymtomatic
22	F	6 6/12	112	18.1	0.74	5	672	Chronic pannephritis
23	M	7	121	23.0	0.88	4	1,149	Eczema
24	F	7 2/12	117	19.9	0.81	4	752	Acute pyelonephritis
25	M	7 6/12	120	20.1	0.82	4	1,104	Cellulitis of nose
26 (*a*)	M	8	103	15.9	0.68	11	438	Chronic pyelonephritis
(*b*)	..	8 5/12	...	17.8	0.67	2	532	Chronic pyelonephritis
27	F	8 1/12	136	35.2	1.12	16	948	Adrenogenital syndrome
28	M	8 9/12	124	24.0	0.91	2	914	Appendectomy
29	M	9 1/12	111	21.1	0.87	61	563	Chronic nephritis
30	F	10 7/12	145	34.0	1.19	5	1,315	No disease
31	F	10 8/12	122	25.8	0.92	6	652	Steatorrhea; vitamin D intoxication
32	M	11 4/12	136	29.0	1.05	5	914	Chronic glomerulonephritis and uremia
33 (*a*)	F	14 3/12	159	55.0	1.55	22	1,146	Rheumatoid arthritis; bedrest, minimal activity
(*b*)	..	14 5/12	159	50.0	1.49	14	909	Bedrest, moderate activity
(*c*)	..	14 7/12	160	53.0	1.53	15	907	Up ad lib.
34	M	14 9/12	140	27.0	1.05	2	739	Asthma; asymptomatic
35	F	15	154	64.1	1.65	2	992	Appendectomy
36	F	16 2/12	136	33.8	1.10	13	836	Rheumatoid arthritis
37	M	18 10/12	156	49.6	1.49	25	650	Chronic glomerulonephritis
38	M	21 1/12	175	56.0	1.70	82	872	Chronic glomerulonephritis
39	M	23 11/12	171	56.8	1.65	25	704	Diabetes mellitus with retinopathy and nephritis

* Surface area was estimated according to the directions of Crawford, J. D.; Terry, M. E., and Rourke, G. M.: Pediatrics 5: 783, 1950.

measured in grams after collection in tared bedpans. Blood withdrawn from the patient for testing was measured by means of standard type syringes, with the total amount in milliliters per study period added to the total output. Other output, gastric drainage, paracentesis fluid, etc., was measured in cylinders, if liquid, or in a manner similar to the stool output, if solid.

I. W. L. was calculated from insensible weight loss according to the directions of Newburgh by

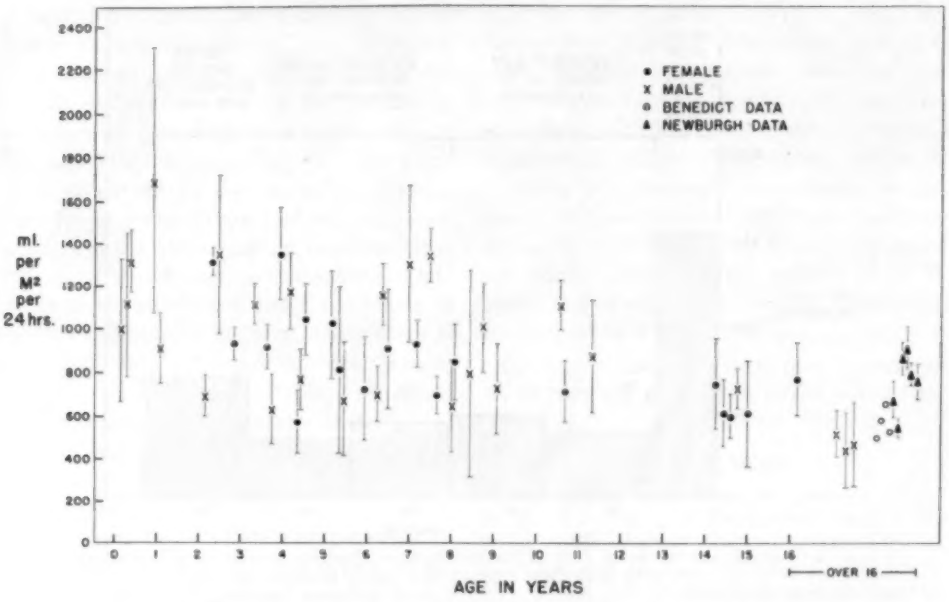


Fig. 1.—Insensible water loss per square meter per 24 hours plotted against age. The symbols represent the average value, and the length of the vertical lines through each symbol give the standard deviation for each patient.

means of the following equation: I. W. L. = insensible weight loss — (CO_2—O_2), where CO_2 is the weight of carbon dioxide expired and O_2 is the weight of oxygen absorbed during the period of insensible-weight-loss measurement.[5] In 18 of the 39 cases, the value for (CO_2 — O_2) was estimated from values for combustion of the carbohydrate, protein, and fat content of the diet as estimated by the metabolic unit dietition. In six cases, the intake consisted entirely of intravenous infusions containing dextrose and electrolytes. In these instances, the carbohydrate intake was readily derived. In the remaining 15 patients, who were on "house diet for age," the I. W. L. was assumed to be 93.5% of the insensible weight loss.[6]

Arbitrarily, 20 hours was selected as the minimum-length single observation which when extrapolated to 24 hours might be included in this study. The majority of the individual observations were actually 24 hours in length. Periods of observation on individual patients ranged from a minimum of 2 to a maximum of 82 days.

Five hundred sixty-four of the 596 measurements were carried out during periods when the patients were afebrile. The remaining 32 measurements were made during intervals when the patients had temperatures ranging between 100 and 104 F. These measurements were scattered approximately evenly through 16 of the 45 periods of study represented in Figure 1.

RESULTS AND COMMENT

The mean I. W. L. value obtained for each patient according to the procedures outlined above is set forth at the right of the Table. As might be expected, there is a tendency for these values to increase as age, height, weight, and body surface area, respectively, increase.

Figure 1 presents these results in terms of milliliter per square meter of surface area per 24 hours (ordinate) with relation to age (abscissa). Data of Newburgh and coworkers [5] and of Benedict and Root,[7] obtained on normal adults, are included at the right of Figure 1. Values for I. W. L. were found to be highest in the first three years of life (average approximately 1150 ml/sq. m/day), decreasing to an average level of about 950 ml/sq. m/day in children 3 to 8 years of age. The average for patients over 8 years old was approximately 700 ml/sq. m/24 hours. The over-all average value for patients between 2 months and 16 years of age (Patients 1 through 36, Table) was 930 ml/sq. m/24 hours.

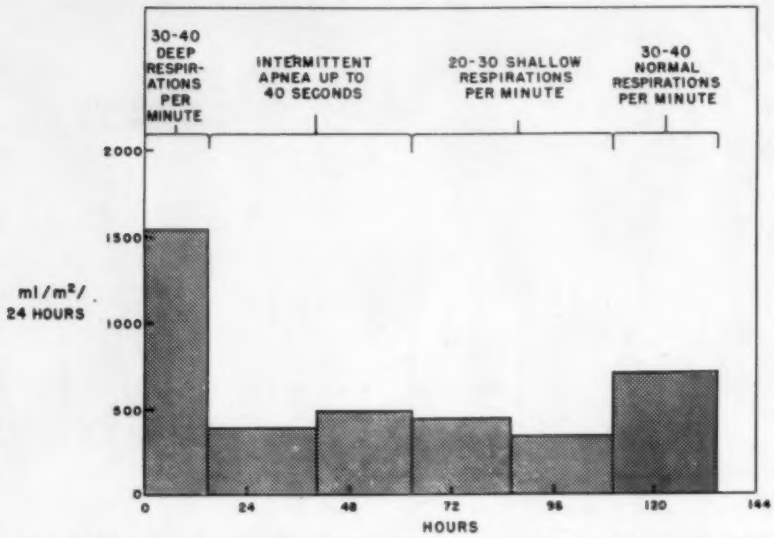


Fig. 2.—Abrupt alterations in rate of insensible water loss in association with changes in respiratory behavior. The subject of these observations was a 14-month-old infant with probable sagittal sinus thrombosis.

The vertical lines representing standard deviation in Figure 1 show that there was a considerable range in the I. W. L. values found over a period of days in individual subjects (average standard deviation, ± 200). Moreover, Figure 2 illustrates the fact that rate of I. W. L. sometimes underwent a marked change in the course of 24 to 48 hours. In the case of the patient of this figure, it appeared that the changes in rate were related to alterations in respiratory behavior, a factor known to be capable of causing large changes in I. W. L.[4]

In 30 instances, when measurements were obtained during intervals when body temperature ranged between 100 and 102.8 F, I. W. L. values did not differ appreciably from those obtained on the same patients during periods when they were afebrile. Two I. W. L. values obtained on patients with temperatures of 103 and 104 F, respectively, though higher than average, fell within the range observed for nonfebrile persons.

It would appear from data recorded in the literature that I. W. L. under basal conditions is nearly the same for patients of all ages, being approximately 600 ml/sq. m/day during the first two years and 500 ml/sq. m/day in patients 2 or more years of age.† It may be seen that these values correspond fairly closely to the levels indicated by the bottom ends of the vertical standard deviation lines of Figure 1. It also is evident that total nonbasal I. W. L. per 24 hours gradually approaches these basal or minimal levels as age increases from 1 to 16 years and over. This observation would appear to fit with the fact that I. W. L. bears a direct relation to energy output,[4] which in turn would appear normally to be appreciably higher in the early years of life.

Considered as a whole, the observations set forth above indicate that it is possible to predict rate of insensible water loss in individual hospitalized patients only within rather broad limits. In considering patients with functionally adequate homeostatic systems, it has been customary in this clinic to assume an average insensible water loss value of 1 L/sq. m/24 hours.‡ The present data would suggest that this value is reasonably close to the mean for persons of all sizes. They also indicate that the actual average rate of insensible water loss by in-

† References 1, 8, and 9.

‡ References 3 and 10.

dividual patients may differ from the aforementioned assumed value of 1 L/sq. m/day by as much as 600 ml/sq. m/day. Experience to date indicates that it is not ordinarily necessary to give detailed consideration to this possibility in providing for the water needs of patients whose neurohypophyseal-renal homeostatic system is functionally adequate. On the other hand, it is of considerable importance to pay close attention to rate of insensible water loss under conditions of anuria or obligatory oliguria, where there is gross reduction or complete obliteration of normal homeostatic capacity to compensate for discrepancies between rate of water input and bodily need for solute-free water.§

SUMMARY

This paper reports 596 measurements of the insensible water loss per square meter per 24 hours by 39 patients ranging in age from 2 months to 23 years living under the nonbasal conditions characteristic of ordinary hospital living. The results obtained indicate a gradual decline in total nonbasal insensible water loss values from an average of approximately 1200 ml/sq. m/day in young infants to approximately 700 ml/sq. m/day in older adolescent and young adult subjects. The over-all average for patients 2 months to 16 years of age was 930 ml/sq. m/24 hours. Three-fourths of the average values obtained for the patients making up this group were within ± 325 ml/sq. m/24 hours of this over-all average value. The fact that rate of insensible water loss of nonfebrile patients may change by as much as 1000 ml/sq. m/24 hours within a day is illustrated by detailed observations on one patient.

CONCLUSIONS

It is concluded from these observations that it is practicably possible to make only an approximate estimate of the total insensible water loss of hospitalized patients. In considering the total water needs of the ordinary patient, whose neurohypophyseal-renal homeostatic system is functionally adequate, an average allotment of 1000 ml. of water per square meter per 24 hours to cover insensible losses would appear reasonable. On the other hand, in patients who have lost the normal capacity to retain and reject water in accordance with homeostatic needs by appropriate adjustments in urine water output it becomes of considerable importance to attempt to estimate insensible water losses as closely as possible, making larger than average water allowances for infants under 2 years and smaller than average allowances for persons over 8 years of age.

Dr. Jane Worcester and Miss Judy Chatfield, of the Harvard School of Public Health, gave advice concerning statistical evaluation of the data.

§ References 2 and 3.

REFERENCES

1. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid, Cambridge, Mass., Harvard University Press, 1950.

2. Kerrigan, G. A.; Talbot, N. B., and Crawford, J. D.: Role of the Neurohypophyseal-Antidiuretic-Hormone-Renal System in Everyday Clinical Medicine, J. Clin. Endocrinol. **1**:265, 1955.

3. Talbot, N. B.; Kerrigan, G. A.; Crawford, J. D., and Cochran, W.: Application of Homeostatic Principles to the Practice of Parenteral Fluid Therapy, New England J. Med. **252**:856 and 898, 1955.

4. Newburgh, L. H., and Johnston, M. W.: The Insensible Loss of Water, Physiol. Rev. **22**:1, 1942.

5. Newburgh, L. H.; Wiley, F. H., and Lashmet, F. H.: A Method for the Determination of Heat Production Over Long Periods of Time, J. Clin. Invest. **10**:703, 1931.

6. Newburgh, L. H.; Johnston, M. W., and Newburgh, J. D.: Some Fundamental Principles of Metabolism, Ann Arbor, Mich., J. W. Edwards Brothers, 1945.

7. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1, 1926.

8. Levine, S. Z., and Marples, E.: The Insensible Perspiration in Infancy and in Childhood: III. Basal Metabolism and Basal Insensible Perspiration of the Normal Infant; A Statistical Study of Reliability and of Correlation, Am. J. Dis. Child. **40**:269, 1930.

9. Ginandes, G. J., and Topper, A.: Insensible Perspiration in Children: II. Statistical Correlation of Insensible Perspiration and Various Body Measurements; Proposed Standards for Children, Am. J. Dis. Child. **52**:1335, 1936.

10. Talbot, N. B.; Crawford, J. D., and Butler, A. M.: Homeostatic Limits to Safe Parenteral Fluid Therapy, New England J. Med. **248**:1100, 1953.

Case Finding in Rheumatic Fever

HELEN M. WALLACE, M.D.
LEAH HOENIG, R.N.
and
HERBERT RICH, New York

One of the basic problems in the administration of a program for handicapped children is that of early case finding, that is, how to identify cases at an early stage so that treatment and preventive measures may be promptly instituted.

In the case of rheumatic fever, a familial susceptibility has been said for many years to have existed. It was therefore decided to apply this well-known epidemiological fact to discover "new" cases of rheumatic fever.

METHODS

1. All children and youths under the age of 20 years who died in 1954 and whose deaths on the death certificates were attributed to rheumatic fever or rheumatic heart disease were used for the study.

2. A study form was devised.

3. A public health nurse visited the family at home approximately three months after the patient's death and completed the study form.

4. The data on the study forms were then tabulated and analyzed.

FINDINGS AND RESULTS

During 1954, there was a total of 42 deaths in childen and youths under 20 years of age in New York City attributed to rheumatic fever or heart disease. Of these 42 deaths, 1 was a death of a nonresident of New York City and was excluded from this study. Of the remaining 41, information was readily obtained from the families of 33 (78%); in 4 instances the family refused; in 3 instances the family had moved and could not be located, and in 1 instance the family denied any history of rheumatic fever or heart disease in the patient or in the family.

The study form contained a question on the presence or absence of rheumatic fever or rheumatic heart disease among family members. Eight of the families (20%) stated that fourteen family members (in addition to the source case who had died) had or had had rheumatic fever or rheumatic heart disease. In this group, the families were definite and specific about the diagnosis in the family members. Four other families (10%) gave histories of five family members which were suggestive of a possible history of rheumatic fever or rheumatic heart disease (e. g., may be cardiac, heart murmur, pains in legs). There was no familial occurrence described by the family in 19 cases (46%). In 10 instances (24%) there was no information (Table).

In some instances, the other familial case was under good continual medical care; in

TABLE 1.—*Familial Occurrence of Rheumatic Fever*

Status		No. of Families	Per Cent
Familial occurrence definite		8	20
In one sibling	2		
In father and brother	1		
In aunt and 2 cousins	1		
In maternal grandmother	1		
In father	1		
In maternal aunt and uncle	1		
In mother, brother, and maternal grandmother	1		
Familial occurrence possible		4	10
Mother may have cardiac disease	1		
Brother has heart murmur	1		
Sibling has pains in legs	1		
Father and sister may be cardiac	1		
No familial occurrence		19	46
Unknown		10	24
Totals		41	100

Submitted for publication Aug. 3, 1955.

From the Bureau For Handicapped Children and Bureau of Records and Statistics, New York City Department of Health.

other instances the other familial case was not under current medical care. Accurate information on the status of medical care was not obtained in all instances. In future follow-up activities more emphasis should be placed on this aspect.

ANCILLARY PERTINENT INFORMATION CONCERNING THE DEATHS

1. *Month of Death.*—An analysis by month of death shows no significant pattern.

TABLE 2.—*Age At Death*

Age at Death, Yr.	Deaths, No.
Under 1	2
1-4	1
5-9	6
10-14	13
15-19	19
Total	41

TABLE 3.—*Period Between First Attack of Rheumatic Fever and Death*

Period, Yr.	Children, No.
Less than 1	6
1	3
2	1
3	2
4	1
6	2
7	3
8	2
9	1
10	1
11	1
12	1
14	1
16	1
No history of R.F.	2
No information	13
Total	41

2. *Age at Death.*—As might be anticipated, most of the deaths occurred in the 10-14 age group (13 deaths) and 15-19 year age group (19 deaths) (Table 2).

3. *Period Between First Known Attack of Rheumatic Fever and Death.*—The average period between the first known attack of rheumatic fever and death was approximately six years. It is interesting that in six instances it was less than one year's duration (Table 3).

4. *Sex.*—There were 23 males and 18 females, not statistically significant.

5. *Race.*—Of the 41 deaths, 23 occurred in whites, 12 in Puerto Ricans, and 6 in Negroes. This breakdown gives the highest mortality in the Puerto Ricans.

6. *Distribution by Health District.*—An analysis by health district gives no significant trend.

7. *Place of Death.*—Of the 41 deaths, 18 occurred in municipal hospitals, 15 in voluntary hospitals, 6 at home, and 2 on the street. The 18 municipal hospital deaths may be interpreted as having occurred in the lower socioeconomic groups.

8. *Environmental Home Conditions.*—It was not entirely possible to obtain complete information on this question because of the frequent moving by some families. The information showed that the home was definitely overcrowded in six instances and was damp in four instances. In addition, sleeping arrangements were overcrowded in 10 instances. Two other families stated that, while their living accommodations were satisfactory now, previously there had been overcrowding or they had had to live in damp crowded furnished rooms.

Of the eight cases where there was a definite familial occurrence and of the four cases where there was a possible familial occurrence of rheumatic fever or rheumatic heart disease, five families live or had previously lived in a crowded home, two families live or had previously lived in a damp home, and in three families the sleeping arrangements were overcrowded.

In regard to the family situation, four families receive assistance from the Department of Welfare, in one family the home situation was stated to be poor, and in one family the parents were separated.

9. *Length of Time Consumed by Field Aspects of Study.*—An average of one and one-half hours was spent in making the home visit in the 32 cases where the information was available. An average of 15 minutes was spent by the field public health nurses additionally on this study.

10. *Value of Visits.*—In 25 cases, the public health nurse stated that the home visits were of value in that she was able to do teaching, offer assistance, or be supportive to the family. In eight instances, the public health nurse felt that the visits were not of value; reasons given were reluctance of family to talk, indifference of family, absence of mother, emotional reaction of family.

In 26 cases, the public health nurse stated that such visits could be helpful in the detection and prevention of rheumatic fever. In three cases, the public health nurse did not feel the visits were valuable in the specific family visited. In two cases, the public health nurse felt the value of the visits was questionable.

The study form asked for comments from the public health nurses in regard to this kind of nursing activity. The most frequent comment was that such visits provide an excellent opportunity for family teaching (nine instances). One public health nurse felt that the timing of her visit was excellent, two nurses felt their visit was made too soon, and a fourth nurse felt her visit was made too late after the death. Two public health nurses suggested a study of each family with a rheumatic fever patient at the time of the first attack of rheumatic fever.

11. *Previous Contact of Families with the Services of the Health Department.*—Of the 41 families, 21 had had previously known contact with the Bureau for Handicapped Children of the City Health Department. In all instances except one, the known contact was because of the rheumatic condition; the one exception was contact with the orthopedic phase of the program because of orthopedic handicaps due to poliomyelitis.

Of the 41 families, 19 had previously used other services of the Health Department. Eleven of these nineteen had used child health stations; the others stated that they had used the venereal disease program (one), tuberculosis program (two), prenatal clinic (one), school health services (three), dental service (one).

COMMENT

The most significant finding in the foregoing is that eight families stated specifically that 14 other family members had or had had rheumatic fever or rheumatic heart disease. Four additional families described five other family members in such a manner that the possibility of rheumatic fever or rheumatic heart disease must be ruled out. Not all of these 19 family members were under continuous medical care. It is recognized that a history of rheumatic fever or rheumatic heart disease, as stated by a family, does not constitute an accurate diagnosis and verification of the diagnosis would be essential. Yet it would seem reasonable to conclude that the questioning of family members of deaths attributed to rheumatic fever or rheumatic heart disease can constitute a sound and productive epidemiological first step in case finding.

Whether such a follow-up of deaths is the best source of case finding or whether there are better sources cannot be answered at this time. It would seem logical to assume that the institution of follow-up of patients at the time of their first attack of rheumatic fever might be more desirable; the difficulty is in the identification of the first attack. A practical suggestion is to initiate follow-up of the patient and his family at whatever point there is contact by a public health agency; this step was recently instituted by the New York City Department of Health as a result of this study. Public-health-nursing follow-up on another basis was instituted by the Bureau for Handicapped Children several years ago on all school children with rheumatic fever or heart disease who were placed on home instruction; results of this step should also be evaluated.

The question of "reporting" of cases of rheumatic fever or rheumatic heart disease to the official health agency should be reopened and reevaluated. For many years, experts in the field have been opposed to the requirement of reporting of this disease for two reasons: (1) because it is difficult in

some instances to make a diagnosis; (2) because there is no single simple diagnostic test. Yet official health agencies have required the reporting of other diseases in conditions which also fail to fulfill these criteria. It would appear that experimental reporting might be tried and might be of some value if it can be supported by certain services: (1) the provision of diagnostic and consultation services of high caliber; (2) the provision of public health nursing supervision and follow-up; (3) the provision of prophylactic drugs free of charge at least to those patients who cannot afford it; (4) the provision of adequate hospital care, after care, and home care services.

It is of some interest that the mortality rate is higher among the Puerto Rican group than among the white group. It has been known for many years that this was true in the Negro, but there have been very few data to support the clinical impression that it was also true in the Puerto Rican who has emigrated to the northern section of this country. Whether the incidence of the disease is actually higher in the Puerto Rican or whether the disease is more virulent is unknown but should be investigated.

The association of rheumatic fever with crowding, dampness in the home, etc. is an old and well-known fact. However, it is of importance to public-health personnel, particularly since in some communities it is possible to improve the housing and living conditions of many families with health problems. Certainly, rheumatic fever and rheumatic heart disease should merit a high priority rating in low-cost housing.

SUMMARY

This report describes the results of follow-up of all deaths in New York City in 1954 in patients under 20 years of age attributed to rheumatic fever or rheumatic heart disease. From the viewpoint of case finding, such follow-up is of value.

Thrombocytopenia and Giant Hemangioma in Infants

THOMAS A. GOOD, M.D.
S. F. CARNAZZO, M.D.
and
ROBERT A. GOOD, Ph.D., M.D., Minneapolis

Thrombocytopenia associated with giant hemangioma in the infant produces a disorder featured by hemorrhagic tendency and the occurrence of bleeding into the hemangioma site. Hemorrhagic manifestations in these patients are frequently severe enough to threaten life, and infants have died of this disease. Weissman and Tagnon [1] recently pointed out that enough cases of thrombocytopenia occurring in conjunction with large hemangiomas have been reported to justify considering the simultaneous occurrence of these disorders in the infant as a clinical syndrome. In spite of the established clinical association, the biologic relationship between the thrombopenia and hemangioma remains obscure, and some authors still consider the simultaneous occurrence of these disorders to be coincidental.

It is the purpose of this paper to summarize reported experience with cases of thrombocytopenia and hemangioma and to report three additional cases of our own. A review of the available literature indicates that a relationship between the hemangioma and thrombocytopenia exists. In this report we shall attempt to demonstrate the nature of this relationship. We interpret our observations as support for the concept that the thrombocytopenia is secondary to the hemangioma and is probaly dependent upon excessive destruction of platelets within the tumor.

Submitted for publication June 17, 1955.

Fellow of the Arthritis and Rheumatism Foundation (Dr. Thomas A. Good).

Markle Scholar in the Medical Sciences, American Legion Memorial Heart Research Professor of Pediatrics (Dr. Robert A. Good).

Aided by grants from the U. S. Public Health Service, the Helen Hay Whitney Foundation, Minnesota Cancer Society, and the American Heart Association.

From the Departments of Pediatrics, University of Utah and the University of Minnesota, and the Pediatric Research Laboratories of the Variety Club Heart Hospital, Minneapolis.

REVIEW

In 1940 Kasabach and Merritt [2] first reported the simultaneous occurrence of thrombocytopenia and giant hemangioendothelioma. Because they believed the tumor in their patient to be malignant they used large doses of x-ray as well as radium implants in its treatment. The tumor regressed, and the platelet count increased to normal levels.

Rhodes and Borrelli [3] then reported the case of a 4-month-old boy with thrombopenia associated with a large hemangioendothelioma of the shoulder and neck. X-ray treatment directed to the lesion resulted in return of platelet count to normal. Subsequently the tumor extended to the back and thrombopenia recurred. Further x-ray therapy directed to the tumor over a six-month period resulted in simultaneous regression of the tumor and abatement of the thrombocytopenia.

A 5-month-old infant with hemangioma reported by Silver, Aggeler, and Crane [4] had no bleeding tendency. The platelet count was normal at 14 months of age. Superficial x-irradiation to the tumor resulted in temporary regression. Six months later, following extension of the tumor to the thorax,

thrombocytopenia and bleeding tendency occurred. No further irradiation therapy was used, and the child died. At autopsy, capillary and cavernous hemangioma were present, as was a massive hemothorax.

Southard and co-workers [5] studied a 21-day-old infant with thrombopenia and a capillary hemangioma fairly well localized to the left lower thigh. The location permitted intensive irradiation through multiple portals over a 17-day period. The tumor regressed rapidly, and the platelet count increased to normal levels. Bogin and Thurmond [6] in the same year reported on a 6-week-old infant with hemangioma of the thorax. Radium therapy was applied to the skin overlying the center of the lesion, and x-rays were delivered to the spleen. Because the thrombopenia persisted, splenectomy was performed. No rise in the platelet count occurred following surgical removal of the spleen. Additional radium therapy was directed toward the hemangioma, and regression of the tumor occurred. Follow-up study five months later revealed a normal platelet count.

Recently two additional cases of giant hemangioma and thrombocytopenia have been reported.[1] In both cases the tumor occurred on an extremity. The first infant, a 9-month-old child, had no bleeding tendency until approximately 8 months of age. Following the development of thrombocytopenic purpura a splenectomy was performed which failed to influence either the platelet count or the purpura. The other child received a small dose of x-rays to the tumor without apparent effect on either the tumor or the platelet count. Subsequently, in both patients spontaneous regression of the hemangioma was associated with increase of the platelet count to normal. A summary of the ob-

TABLE 1.—*Summary of Cases of Thrombocytopenia and Hemangioma*

Author	Patient's Ages	Site	Type	Platelet Count	Treatment	Course
Kasabach & Merrit, 1940 (1 case)	2 mo.	Thigh and leg	Hemangio-endothelioma	16,000	300 r/a. to entire thigh, leg, buttock	Platelet count remained down until after radium implant; returned to normal following regression of the tumor
	21 mo.			324,000	878 mg.-hr. radium to lesion	
Rhodes & Borrelli, 1944 (1 case)	4 mo.	Shoulder, back, and neck	Hemangio-endothelioma	Low 15,000	220 r	No effect
	6 mo.			240,000	500 r over 2 mo. period to entire left neck, shoulder	Regression of tumor, platelet count rose
	9 mo.			20,000	4 treatments of 275 r each over 3-mo. period	Progression of tumor, platelet count fell
	18 mo.	Arm and shoulder		450,000	275 r to arm and shoulder	Regression of tumor, platelet count rose
Silver and co-workers, 1948 (1 case)	5 mo.	Back, neck, and face	Capillary and cavernous hemangioma		400 r to back	Temporary regression of tumor
	11 mo.				120 r to neck	No response
	18 mo.			260,000	None	Tumor progressing, platelet count fell; hemothorax, death
	21 mo.			32,000	Transfusions	
Southard and co-workers, (1 case)	21 days	Thigh	Capillary hemangioma	25,000	Transfusions	Rapid regression of tumor, platelet count rose
	50 days			50,000	3300 tissue r	
	60 days			175,000	(cross fired)	
Bogin & Thurmond (1 case)	6 wk.	Thorax	Hemangioma; no biopsy	22,700	300 mg.-hr. radium to lesion, 100 r to spleen	No response in tumor or thrombocytes
	10 wk.			8,380	300 r to spleen	No response in tumor
	3½ mo.			15,040	Splenectomy	
				19,400	300 mg.-hr. radium to each side of lesion	Regression of tumor after irradiation
	8 mo.			136,320		Platelet count rose
Weissman & Tagnon, 1953 Case 1	9 mo.	Forearm	Hypertrophic hemangioma	8,000	Splenectomy	No platelet response after splenectomy
	16 mo.			18,000	Follow-up	Spontaneous regression of tumor; platelet count rose
	2½ yr.			218,000	Follow-up	
Case 2	3½ mo.	Arm	Hypertrophic hemangioma	19,000	300 r (air) to tumor	No response in tumor
	6 mo.			80,000	Follow-up	No change in tumor
	8 mo.			200,000	Follow-up	Spontaneous regression of tumor; platelet count rose

servations on the cases from the literature is included in Table 1.

OBSERVATIONS

During the past several years we have studied three patients having a combination of giant hemangioma and thrombocytopenia. Each of these patients had a large tumor involving the skin as well as subjacent soft tissues. In one instance the tumor occurred on the face and neck, in another on the leg, and in the third on the thorax. All three patients were referred to our hospital because of hemorrhagic manifestations, as well as the unusual appearance of the tumor.

One of the patients died five months following splenectomy performed in an attempt to allay the thrombocytopenia. The autopsy findings as well as the terminal clinical course were interpreted as indicating that death was due to overwhelming sepsis. In two patients

TABLE 2.—*Megakaryocytes in Patients with Giant Hemangioma and Thrombocytopenia*

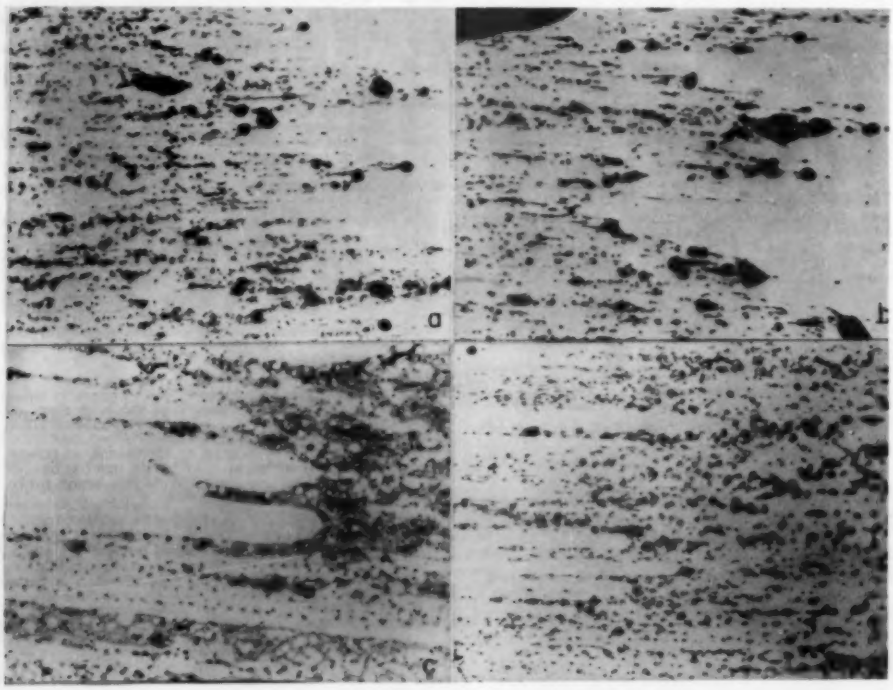
Patient	Age	Sex	Megakaryocytes, 18×18 Mm. Sq.*	Left Shift Megakaryocytes	Developmental Arrest†
Thrombopenia-hemangioma syndrome group					
T. G.	8 wk.	M	439	++	±
C. L. F.	5 mo.	F	935	+++	++
G. C.	3½ mo.	M	619	++	+
Normal infants group ‡					
A. C.	8 mo.	F	90	.....	.....
S. W.	10 mo.	M	126	.....	.....
Essential thrombopenic purpura group					
R. S.	7 mo.	M	728	++	++
T. W.	3 yr.	F	415	++	+++
Refractory anemia group					
J. W.	5 yr.	F	18	.....	.....
Refractory anemia with thrombocytopenia					

* The number of megakaryocytes is determined by a count of all the megakaryocytes found in a terminal 18×18 mm. square on the slide made from a direct smear of the first 0.1 cc. of aspirated marrow.

† Based on morphological features of megakaryocytes originally described by Dameshek and Miller.[7]

‡ Infants admitted to the hospital for surgical correction of cleft lip.

Fig. 1.—Comparison of numbers of megakaryocytes in the bone marrow of patients with essential thrombopenic purpura (*a*); thrombopenia-hemangioma syndrome (*b*); refractory anemia with thrombopenia (*c*); and normal child (*d*). In each figure the feathered edge of the marrow smear is illustrated; reduced approximately ¼ from mag. × 70.



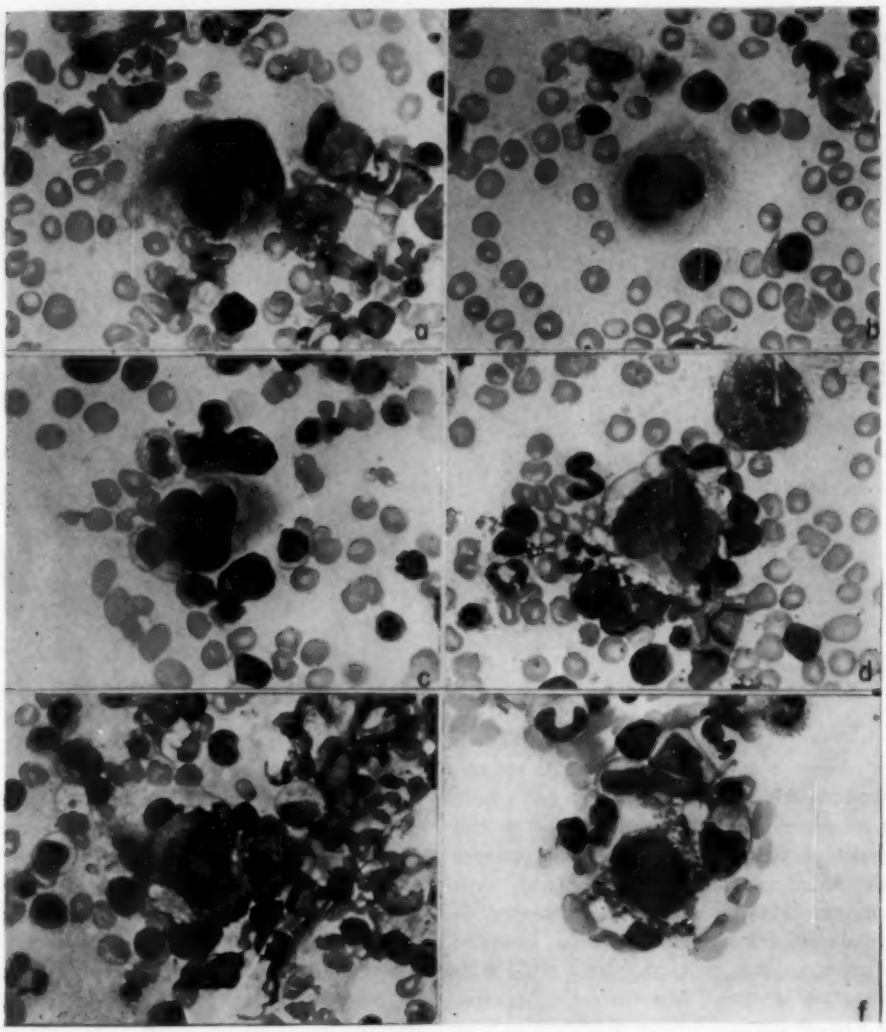


Fig. 2.—The left shift and the "developmental arrest" of the megakaryocytes from a patient with the thrombopenia-hemangioma syndrome. Immature megakaryocytes are illustrated in (*a*), (*b*), and (*c*), and a typical "arrested" megakaryocyte in (*d*) and (*e*). A mature megakaryocyte actively releasing platelets from the marrow of a normal child (*f*).

the giant hemangiomas were successfully treated. In each case the platelet count returned promptly to normal following subsidence of the hemangiomas. In one instance x-irradiation to the tumor alone resulted in a cure of both thrombocytopenia and the hemangioma. In the other patient successful treatment was due to x-ray therapy combined with surgical excision of the tumor.

Bone-marrow biopsies were performed on each of our cases and specimens of the tumor were available in two instances, sections from tissue excised surgically in one and necropsy specimens of the tumor on the third. The bone-marrow studies revealed an essentially normal marrow except for evidence of response to blood loss and abnormalities in the numbers and morphology of the platelets and megakaryocytes. Increased numbers of megarkaryocytes with a shift to the left of the megakaryocytes were observed in each instance, and clear evidence

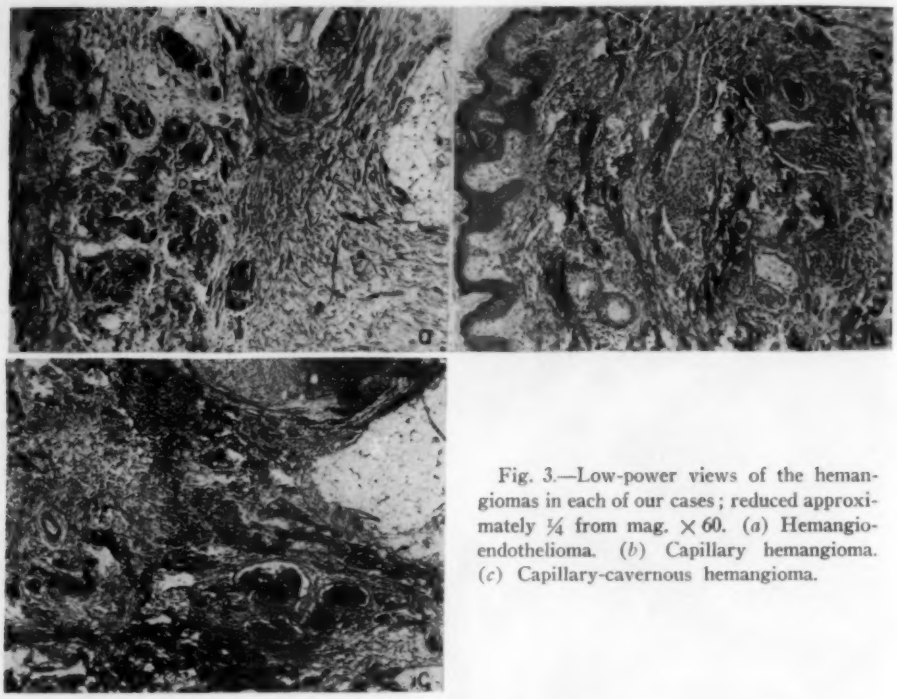


Fig. 3.—Low-power views of the hemangiomas in each of our cases; reduced approximately ¼ from mag. × 60. (*a*) Hemangioendothelioma. (*b*) Capillary hemangioma. (*c*) Capillary-cavernous hemangioma.

of the "megakaryocyte arrest" of Dameshek was observed in two cases. The latter observations are summarized in Table 2, where the numbers and the morphology of the megakaryocytes in the marrow of patients with hemangioma-thrombocytopenia syndrome are compared to those observed in normal children, children with essential thrombocytopenic purpura, and a child with "refractory anemia" and thrombocytopenia. On Figure 1 a low-power view of the bone marrow from a patient with thrombocytopenia and giant hemangioma is compared to a similar view of the marrow of a normal child, a child with chronic idiopathic thrombocytopenic purpura, and one with refractory anemia and thrombopenia. In the patient with essential thrombocytopenic purpura and in the patients with hemangioma and purpura the increased number of megakaryocytes is readily apparent, whereas only few megakaryocytes were present in the feathered edge of the marrow smear of the normal child and virtually none were seen in a comparable area of the marrow in the patient whose thrombopenia was associated with refractory anemia. In Figure 2 are shown megakaryocytes from one of our hemangioma cases. The cells illustrated were present in abundance in this child's marrow and are typical of those Dameshek and Miller [7] described in proposing their concept of developmental arrest of megakaryocytes in essential thrombocytopenic purpura. Shown for comparison is a megakaryocyte from the marrow of a normal child. The cell illustrated is mature and is actively engaged in the process of platelet formation.

Microscopic studies of the hemangiomas were made in each of our cases. A medium-power view of the three tumors is shown in Figure 3. The microscopic structure was designated by pathologists as hemangioendothelioma in Case 1, capillary hemangioma in Case 2, and capillary and cavernous hemangioma in Case 3.

The biopsy material from each patient was stained with Wright's platelet stain as well as hematoxylin and eosin, and in each instance many of the vessels of the hemangioma

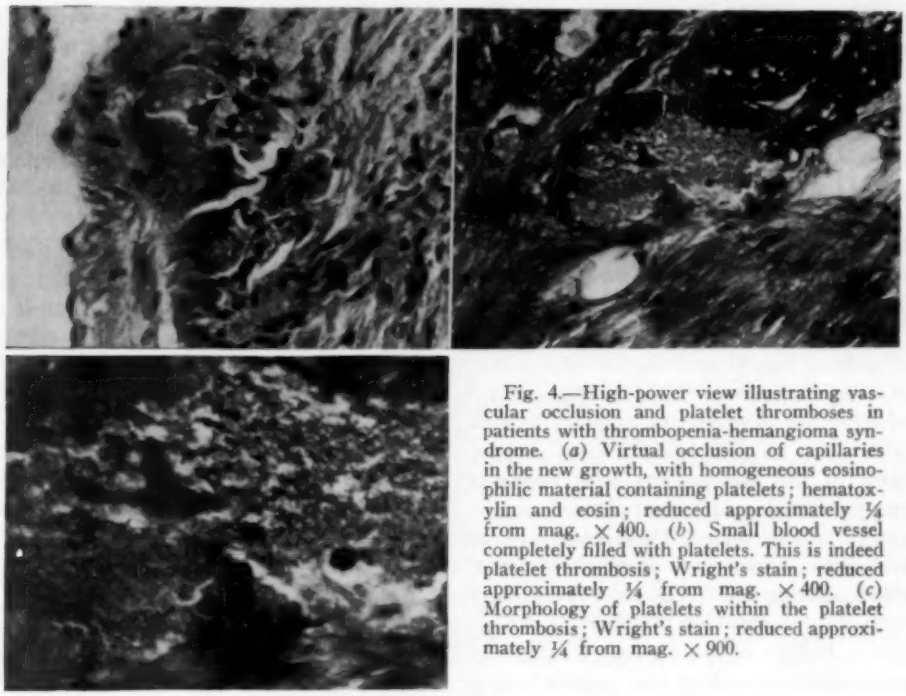


Fig. 4.—High-power view illustrating vascular occlusion and platelet thromboses in patients with thrombopenia-hemangioma syndrome. (*a*) Virtual occlusion of capillaries in the new growth, with homogeneous eosinophilic material containing platelets; hematoxylin and eosin; reduced approximately ¼ from mag. × 400. (*b*) Small blood vessel completely filled with platelets. This is indeed platelet thrombosis; Wright's stain; reduced approximately ¼ from mag. × 400. (*c*) Morphology of platelets within the platelet thrombosis; Wright's stain; reduced approximately ¼ from mag. × 900.

TABLE 3.—*Laboratory Data*

Patient	Date	Hemoglobin, Gm./100 Cc.	Platelets/ Cu. Mm.	Treatment
T. G.	11/25/49	8.9	22,000	.....
	12/ 1/49	7.9	72,000	Transfusions (100 cc. × 3)
	12/ 2/49	7.0	48,000	Splenectomy
	12/ 5/49	9.3	32,000	300 cc. whole blood
	12/ 9/49	11.2	30,000	.....
	12/27/49	9.1	65,000	.....
	1/16/50	9.2	58,000	.....
	4/24/50	11.2	24,000	Death with overwhelming infection and adrenal hemorrhage
C. L. F.	4/30/50	8.9	35,000	.....
	5/ 9/50	10.7	10,000	100 cc. whole blood
	5/11/50	...	12,000	End of first series of irradiation to thigh, leg, spleen
	5/15/50	10.1	22,000	Splenectomy
	5/17/50	8.6	30,000	200 cc. whole blood
	6/ 7/50	8.5	44,000	120 cc. whole blood, second series x-ray to thigh, leg
	7/17/50	11.2	76,000	.....
	10/30/50	...	.....	X-ray to thigh and leg
	12/20/50	12	206,000	Transfusions
	12/29/50	13.5	.....	Surgical removal of hemangioma of thigh, Stage 1
	2/ 9/51	...	212,000	Transfusions
	2/19/51	...	.....	Surgical removal of hemangioma of thigh and leg, Stage 2
	2/24/51	12.3	160,000	.....
G. A. C.	9/25/52	5.3	18,000	300 cc. whole blood
	10/ 3/52	12.3	42,000	End first series x-ray therapy
	10/ 5/52	13.2	70,000	.....
	10/ 7/52	10.1	28,000	.....
	10/24/52	11.1	30,000	75 cc. whole blood
	10/27/52	11.3	40,000	.....
	10/31/52	11.7	60,000	.....
	11/ 3/52	....	88,000	.....
	11/ 4/52	12.3	27,000	.....
	12/ 2/52	12.7	80,000	.....
	12/ 5/52	....	.....	End second series of x-ray therapy
	12/ 9/52	....	52,000	.....
	12/11/52	12.0	106,000	.....
	12/16/52	11.3	150,000	.....
	1/ 6/53	11.1	206,000	.....
	2/ 3/53	....	145,000	.....
	3/17/53	....	254,000	.....

were found to be filled with platelet thrombi. The appearance of this form of intravascular thrombosis in material stained with hematoxylin and eosin and Wright's stain is illustrated in Figure 4*a*. Some of the thrombi were homogeneous. In others the material deposited seemed to be granular in nature. In all, intensely eosinophilic material reminded of "fibrinoid" was noted. That the thrombi contain abundant platelets was repeatedly observed. In many instances the thrombi were found to be composed almost entirely of platelets (Fig. 4*b* and *c*).

As may be seen in Table 3, splenectomy performed in two of our cases had no demonstrable effect on the platelet count, whereas control of the hemangioma with roentgen therapy resulted in abatement of the thrombopenia in two instances. These observations, taken with experience already reported, Table 1, indicate that splenectomy is regularly unsuccessful in relieving this form of thrombopenia. Failure of splenectomy to alter the thrombopenia in each of four cases where it has been tried is strong evidence that splenectomy is of no benefit to these patients and should not be performed in this disease. On the other hand, spontaneous regression (2 of 2 cases, Table 1), surgical excision (1 of 1 case, Table 3), or successful irradiation (6 of 6 cases, Tables 1 and 3) of the hemangioma regularly resulted in return of the platelet count to normal. It seems clear from these observations that regression, elimination, or destruction of the hemangioma regularly results in abatement of the thrombopenia. The observations presented to date, therefore, suggest that roentgen therapy directed toward the tumor is the treatment of choice for this symptom complex.

REPORT OF CASES

T. G., an 8-week-old boy, was first seen at the University of Minnesota Hospitals on Nov. 14, 1949, with the chief complaint of a mass on the right side of the face and neck which had been noticed for about six weeks. Black-and-blue discoloration in and surrounding the mass had developed in the two weeks prior to admission. Gestation, birth, and family histories were negative. Physical examination revealed a large, fairly well-defined mass measuring approximately 7×7 cm. covering the angle of the right jaw from the parotid region down into the neck (Fig. 5). Hemorrhage was present in the skin over and around the mass, and many petechiae were present on the neck and chest. The mass was soft and fluctuant but was neither warm nor tender. The spleen was

Fig. 5 (T. G., thrombopenia-hemangioma syndrome).—Hemangioma occupying the parotid and neck region. Note the large size of the mass and the discoloration due to hemorrhage within the tumor.

not palpable. Laboratory study showed the hemoglobin to be 9.7 gm. per 100 cc. Leucocyte count was 6650, with 29% neutrophiles, 55% lymphocytes, 7% monocytes, and 9% eosinophiles. The platelet count was 22,000. Skull x-rays and x-rays of the face showed no bony involvement. The soft-tissue swelling represented by the mass was observed on the roentgenogram. No calcification was present.

Hematological examination revealed few platelets to be present in the peripheral smear but showed no significant morphological abnormalities among the red or white cells. Bleeding time (Duke) was six minutes, and capillary tube clotting time was three minutes (normal). Prothrombin time was normal. Bone marrow aspirations taken on Nov. 29, 1949, from both iliac and sternal sites were interpreted as revealing a general increased cellularity and increased numbers of marrow cells, especially the red blood cell series. In addition, the marrow showed increased numbers and left shift of the megakaryocytes. Biopsy of the tumor was deferred because of fear of severe hemorrhage.

Based on these findings it was the clinical impression that in this patient essential thrombocytopenia was associated by chance with a large hemangioma. During several weeks of observation, although the child's general condition seemed to be satisfactory, the mass fluctuated in size. However, in December, 1949, severe bleeding occurred, and splenectomy was performed. Following splenectomy the platelet count did not rise and the hemorrhagic tendency persisted. The child continued to bleed into the tumor, and several transfusions were required to prevent exsanguination. The tumor mass enlarged markedly and at times even threatened the airway. However, bleeding finally subsided, and the mass spontaneously decreased somewhat in size. With this temporary regression of the tumor the platelet count rose to 65,000. The child's condition stabilized, and a gradual decrease in the size of the mass was noted. However, the platelet count remained low. X-ray therapy was considered, but none was given, and the child was discharged on Jan. 28, 1950. Hematological investigation performed after splenectomy revealed evidence of mild macrocytic anemia, reticulocytosis, basophilic stippling in the erythrocytes, and a few normoblasts in the peripheral smear. The bone-marrow aspiration showed very little change from the presplenectomy bone marrow aspiration. The marrow was hyperplastic, with an increase in normoblastic series and a slight decrease in neutrophiles and their precursors. The eosinophiles were increased (4.8%), and the megakaryocytes were relatively numerous, with a shift to the left. Evidence of platelet formation was minimal.

Follow-up examination in the pediatric clinic on April 24, 1950, showed the child to be doing well. The mass was smaller, firmer, and more circumscribed than previously, and there was less discoloration surrounding it. The hemoglobin was 11.2 gm. per 100 cc., and the platelet count was 24,000. Leucocyte count was 24,000, with 43% neutrophiles, 49% lymphocytes, 4% monocytes, and 4% eosinophiles. Physical examination was negative except for the mass.

It was planned that the child be followed carefully by his family physician and be brought to the hospital three months hence for removal of the tumor. On May 9, 1950, he suddenly developed irritability, anorexia, and vomiting, followed by high fever, cyanosis, and prostration. Death ensued 18 hours after the onset of the acute febrile illness in spite of treatment with chloramphenicol (Chloromycetin) and penicillin. The gross autopsy done by the local physician was reported to reveal tumor of the right side of the neck and congestion of the lungs. No accessory spleens were found.

Microscopic sections were studied by the University of Minnesota Pathology Department. The tumor was found to be a hemangioendothelioma which was well encapsulated. Although in several areas it seemed to be penetrating into the capsule it was considered to be benign. Areas of hemorrhage and necrosis in the tumor were seen. Sections of the lung showed mild edema and atelectasis, and the adrenal glands were hemorrhagic. These findings were interpreted as being consistent with the occurrence of overwhelming bacterial infection. Explanation for the thrombocytopenia was not found. There was no evidence of lymphoblastoma. Reexamination of the tumor in light of subsequent cases revealed numerous areas of thrombosis within the vessels of the tumor. The latter have been shown to contain many platelets.

C. L. F., a 5-month-old white girl, was admitted to the University of Minnesota Hospitals on April 29, 1950, with the chief complaint of swelling and purple discoloration of the left lower extremity, present since the patient was 3 months of age. Gestation was normal but had been terminated by Caesarean section. A small red "birth mark" on the medial aspect of the left knee was noted in the neonatal period. This lesion began to enlarge shortly after birth and continued to grow until one week prior to admission to the University of Minnesota Hospitals, when the extremity rapidly became swollen and discolored. Anemia developed, and transfusions were given. Family history was negative for bleeding tendency. Physical examination revealed an alert, 5-month-old girl with a markedly swollen left lower extremity in which induration and discoloration extended from the inguinal ligament to the foot (Fig. 6). On the lateral aspect of the leg and thigh, discoloration in various shades of purple, brown, and green provided evidence of recent hemorrhage into the

Fig. 6 (C. L. F., thrombopenia-hemangioma syndrome).—(*a*) Note the huge discolored tumor occupying virtually the entire left leg of the patient. (*b*) Appearance of the child in 1954, three years after combined x-ray and surgical treatment. Both the hemangioma and the thrombopenia have been cured.

soft tissue of the extremity. Ulceration was present on the medial aspect of the knee. The nail beds of the toes were normal in color. The liver and spleen were felt at the right and left costal borders, respectively. Admission laboratory studies demonstrated a hemoglobin of 8.9 gm. per 100 cc. and a normal leucocyte count, with a slight eosinophilia. Urinalysis was negative. The platelet count was 35,000 on admission and ranged between 10,000 and 76,000 during the child's hospitalization. Bleeding time was prolonged to 10 minutes (Duke), and clot retraction was very poor in 24 hours. The Rumpel-Leede cuff test was negative. A bone-marrow aspiration from the iliac crest was interpreted as showing generalized hyperplasia of the cellular elements, with increase particularly in normoblastic elements (42.6%). The neutrophiles and their precursors were decreased (13.6%), and there was a slight increase in eosinophiles (4.6%) and myeloblasts (2.2%) and normal numbers of basophiles. The megakaryocytes and their precursors were markedly increased in number, and a shift to the left was observed. Very few megakaryocytes seemed to be forming platelets, and platelets were extremely scarce. Centrifuged marrow showed the following components: fat, trace; plasma, 62.5%; myeloid-erythroid, 11.0%; erythrocytes, 26.5%. Peripheral blood morphology showed only minimal morphological abnormalities in the red blood cell series, and very few platelets were visible on the smear. The diagnosis of giant hemangioma occurring together with essential thrombocytopenic purpura was made on the basis of these findings. Supportive treatment consisted of transfusions, small doses of oral penicillin and rutin and elevation of the extremity. Biopsy revealed the tumor to be a capillary hemangioma with many angiomatous spaces filled with blood. On May 6, 1950, the first of three series of x-ray treatments was begun. Roentgenological data for these treatments is given in Table 2. Following this first series of irradiation treatments the hemangioma seemed to regress and the leg became less edematous and discolored. The thrombocytopenia persisted, however, and on May 15, 1950, the spleen was removed. At this operation, in addition to the normal-appearing spleen, a small accessory spleen was identified and removed. The postoperative period was stormy. Bleeding occurred into the tumor and surrounding tissues, and blood transfusions were required to maintain the hemoglobin level above 8.5 gm. per 100 cc. The platelet counts preceding splenectomy were 10,000 to 22,000 and in the 10 days following splenectomy ranged from 12,000 to 44,000. These data are interpreted as indicating that no significant change in platelet count resulted from splenectomy. There was very little change in the condition of the extremity. In June of 1950 we discovered the paper of Kasabach and Merritt reporting the excellent response to x-ray treatment, and further radiation therapy was directed to the tumor.

After the second series of x-ray treatments most of the discoloration and brawny edema disappeared, and the tumor consisted of two fairly distinct areas of tissue, one around and below the knee and one in the midthigh. The platelet count rose to 76,000

four days following the completion of the second series of irradiation treatments (June 14, 1950). Two small blood transfusions brought the hemoglobin to 13.9 gm. per 100 cc., and the child was discharged on June 15, 1950, to return to the pediatric clinic for follow-up and further x-ray therapy. One month later the child was seen in the outpatient clinic. She had been doing well. The tumor, although still present, was smaller than it had been at hospital discharge, but the platelet count had dropped again to 46,000. Further x-ray therapy was planned, and on Oct. 30, 1950, she received superficial x-ray therapy to the tumor in a dosage of 200 r in air. Because of the expense of travel from Omaha to Minneapolis the patient's family decided to have the patient treated by the family physician, who elected to complete the treatment by surgical excision of the hemangioma.

On Dec. 17, 1950, the child was admitted to St. Joseph's Hospital in Omaha because of recurrence of swelling and discoloration of her left lower extremity. On examination the extremity was severely swollen and the skin surface was covered with petechiae. The popliteal space was uniformly discolored bluish-black and contained freshly extravasated blood. Laboratory work-up showed the hemoglobin to be 12 gm. per 100 cc., the leucocyte count 14,000 with a normal differential, and the platelet count 205,000. The clot retraction was poor in 24 hours, but a repeat platelet count on Dec. 21 was 228,700. Bone-marrow aspiration was interpreted to show erythroblastic type of marrow commonly seen in anemias due to the blood loss. Biopsy of the tumor of the thigh again demonstrated it to be a capillary hemangioma. The hemangioma was removed surgically in two stages and the area repaired in the third stage. Clot retraction had returned to normal on Dec. 29, 1950. Removal of the hemangioma of the thigh (first stage) was performed on Jan. 2, 1951, with primary closure of the defect without grafting. On Feb. 9, 1951, bleeding again occurred into the leg, and a second operation for the removal of the hemangioma of the medial part of the popliteal space and upper leg was done. At surgery dissection was carried odwn to the muscles, and the major part of the hemangioma was excised. Further removal was not attempted. Laboratory studies during this admission showed the platelet counts to be in the low normal range (160,000 to 212,000). On March 18, 1951, split-thickness grafts were applied, and the child recovered uneventfully and was discharged on April 1, 1951. Since that time she has required no further hospitalizations. However, on several occasions minor bleeding into the remaining hemangioma sites has occurred. Her mother reported that some swelling and bluish discoloration in the tumor area occurred in the summers of 1951, 1952, and 1953. Platelet counts taken on several of these occasions and at other times during follow-up clinic visits have been reported by the family physician to be normal. The child was seen on Sept. 27, 1954, by one of us (T. A. G.). She has been free of hemorrhagic manifestations for more than a year. Although slight contracture of the scars in the surgical sites which tended to produce a slight flexion of the knee and mild external rotation of the foot was present, she could walk and run well without limping. The final result of her treatment is illustrated in Figure 6*b*.

G. A. C., a 3½-month-old boy, was admitted to the University of Minnesota Hospitals on Sept. 25, 1952. One month prior to admission his mother had noticed a small black-and-blue mark about the size of a quarter, which appeared in the left axilla. The area had gradually increased in size until almost the entire hemithorax was covered by the hematoma. In addition, discoloration of the right side of the thorax had occurred in the week preceding admission. There was no history of trauma, and aside from this lesion the child had been well. The past medical history was noncontributory. The infant had been born prematurely, terminating an otherwise uneventful pregnancy. Birth weight was 1940 gm. No evidence of bleeding tendencies was found in the family history.

Physical examination revealed a pale, irritable infant with bluish-black discoloration of the entire thorax. The darkest area was under the left axilla, and the color faded to bluish-brown in the right anterior thorax. The discoloration and brawny edema were sharply limited to the thorax (Fig. 7). The skin of the chest was leathery to touch except in the left axilla, where two fluctuant areas about 2.5×2.5 cm. were found. Petechiae were observed on the face, abdomen, and extremities. Neither the spleen nor the liver was palpable. Laboratory studies revealed a marked thrombocytopenia and anemia, the platelet count being 18,000 and the hemoglobin 5.3 gm. per 100 cc. The erythrocyte count was 1,940,000 and the hematocrit 17.5%. The leucocyte count was 12,250, with 46% neutrophiles, 51% lymphocytes, 2% monocytes, and 1% basophiles. The urinalysis was negative. The reticulocyte count was 7%. Bleeding time (Duke) was over 15 minutes, and bedside clotting time was 4 minutes. A Rumpel-Leede test was strongly positive. Bone-marrow aspiration done on Sept. 26, 1952, was interpreted as being markedly hyperplastic. Normoblasts were relatively increased (34.6%); neutrophiles and their precursors showed no alteration in number or morphology (35.0%). There was a slight absolute increase in the numbers of eosinophiles, and the megakaryocytes appeared to be increased and to show normal morphology except for a moderate shift to the left. There was no evidence of lymphoblastoma.

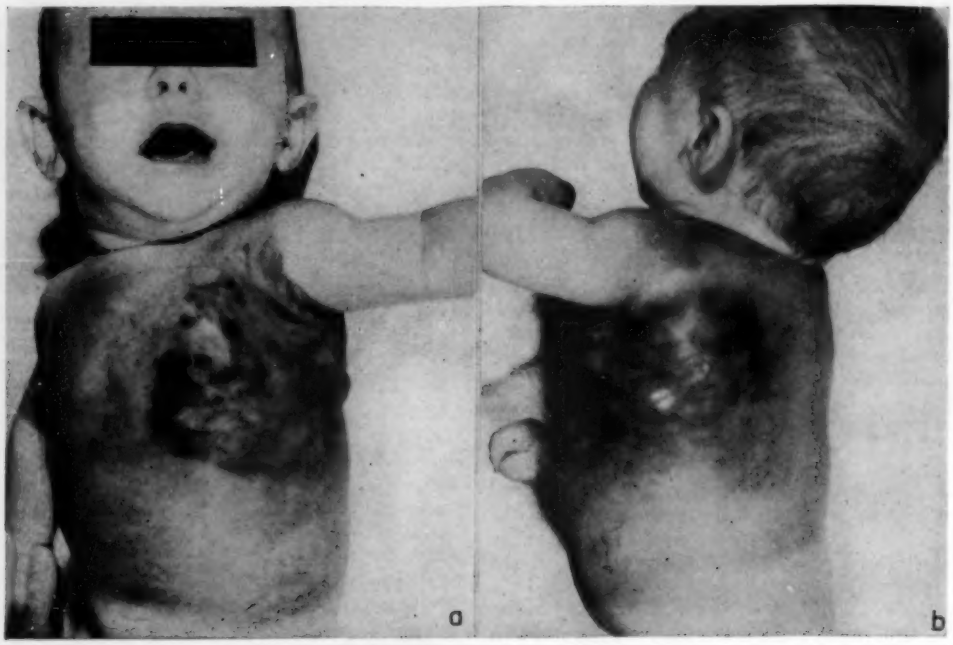


Fig. 7.—Giant hemangioma of the thorax associated with thrombocytopenic purpura. Prior to x-ray treatment, (*a*) and (*b*), note the huge hemangioma on the left side of the thorax surrounded by extensive intracutaneous and subcutaneous hemorrhage over the entire thoracic cage. (*c*) Following x-ray therapy, note the complete destruction of the hemangioma. Only residual pigmentation from the x-ray therapy remains. The thrombopenia has been cured.

A punch biopsy specimen was taken from the left lower axilla. Biopsy of the center of the lesion was deferred because needle aspiration produced venous blood similar to that obtained from a venous puncture.

The diagnosis of thrombocytopenia associated with a hemangioma was advanced, and the child was given transfusions and x-ray therapy. The first of two series of superficial x-ray treatments was started on Sept. 27 and completed on Oct. 3, 1952 (Table 3). Following this x-ray treatment the lesion regressed considerably, and the color changes on the thorax were typical of extravasated blood. The lesion in the axilla became less fluctuant, and it became evident then that the center of the hemangioma was in the middle of the left axilla. The child's general condition remained stable, and the hemoglobin levels were maintained without further transfusion. Because of the persistence of the thrombocytopenia, a trial of 10 mg. of corticotropin (ACTH) intramuscularly was given every six hours for 10 days, from Oct. 21 to 31. The platelet count showed a gradual rise from 18,000 to 88,000 while the child received this drug. Bone-marrow aspiration was repeated following the corticotropin therapy and showed very little change from the first bone-marrow specimen taken at the

time of admission. A surgical biopsy specimen was taken from the center of the lesion on Nov. 5, 1952. After the biopsy a hemorrhage occurred into the subcutaneous tissues. The platelet count dropped to 27,000, but the hemoglobin remained stable. The tumor appeared to increase in size. Splenectomy was considered, but in view of the poor results observed in our two previous cases and the result reported by Bogin and Thurmond,[6] as well as Weissman and Tagnon,[1] splenectomy was deferred. The second series of superficial x-ray treatments was started on Nov. 20, 1952. Sixteen treatments, each delivering 150 r in air to the left anterior and posterior aspects of the left thoracic area, were given. During the last half of the treatment the lesion began slowly to regress. The platelet count remained very low (16,000 to 30,000) until four days following completion of the irradiation therapy, on Dec. 5, 1952. Within six days following completion of x-ray therapy the platelet count had risen to 106,000. During the subsequent 10 days marked regression of the tumor occurred, and the child was discharged from the hospital. He was seen again in the outpatient clinic, where the tumor was noted to be smaller and the platelet count was 200,000. On the final visit, in March, 1953, the child was well, the hemangioma had disappeared, the only remnant being a fibrous mass covered by skin featured by mild residual pigmentation. The platelet count was 264,000. The healed lesion is illustrated in Figure 7*c*. The details of the irradiation therapy given to our patients are summarized in Table 4.

TABLE 4.—*Irradiation Therapy Details**

	Dates	Field Treated	Dose in Air, R	No. Treatments	Kilovoltage	Half-Value Layer	Distance, Cm.
Case 2	5/ 6 to 5/11/50	Anterior spleen	50	2	220	1.35 mm. Cu	60
C. L. F.		Ant. lt. leg & thigh	75	2	220	1.35 mm. Cu	60
		Med. lt. leg & thigh	75	2	220	1.35 mm. Cu	60
	6/ 7 to 6/10/50	Med. upper lt. leg, thigh	100	2	220	1.35 mm. Cu	60
		Post. upper lt. leg, thigh	100	2	220	1.35 mm. Cu	60
	10/30/50	Post. oblique lt. leg, thigh	200	1	140	4.2 mm. Al	60
Case 3	9/27 to 10/ 3/52	Left axillary area	150	4	100	2.4 mm. Al	60
G. A. C.	11/20 to 12/ 5/52	Ant. lt. chest	150	3	140	4.2 mm. Al	60
		Post. lt. chest	150	4	140	4.2 mm. Al	60
		Lat. lt. chest	150	2	140	4.2 mm. Al	60

* Irradiation was applied to the local lesions with x-ray beam fields large enough to cover the entire involved area. Small total doses were used. Radiation detail by Donn G. Mosser, Radiation Therapist, University of Minnesota.

COMMENT

Diagnosis of the hemangioma-thrombopenia syndrome may be made by inspection if one realizes that thrombopenic purpura and hemangioma occur together and may be related. In our patients the diagnosis was, in each instance, stumbled upon in the course of a frantic work-up of an unusual case, even though the patients were seen by numerous attending pediatricians, surgeons, and dermatologists at the University of Minnesota Hospitals. Obscuring the hemangioma, the bleeding sometimes makes recognition of it difficult. The occurrence of maximal hemorrhage at the tumor site leads one to consider local factors rather than blood dyscrasia to be responsible for the bleeding tendency. As Kasabach and Merritt[2] pointed out, the similarity of the appearance of the lesion observed in these patients to that of a violent malignant condition necessitates biopsy in spite of the risk of hemorrhage. Even though biopsy is somewhat dangerous, e. g., Case 3 in our series, successful management of the tumor is dependent on a morphological diagnosis, and the procedure should be performed. Studies of platelet counts and the morphology of the peripheral blood and bone marrow aspirations revealing an isolated deficiency of platelets associated with megakaryocytic hyperplasia are helpful in establishing the diagnosis and ruling out other disturbances in the hematopoietic system which might be confused with this syndrome. Cellulitis or thrombophlebitis usually may be excluded by absence of local or general signs of infection. However, in two of our three cases a marked leucocytosis associated with hemorrhage into the tumor served to confuse the diagnosticians. The danger from bleeding into these tumors is real. In two of our cases

virtual exsanguination occurred, necessitating transfusions to sustain life, and in one instance bleeding into a hemangioma in the neck threatened the airway.

Following an unsuccessful attempt to treat the thrombocytopenia by splenectomy, our first patient died with an acute infection associated with hemorrhagic pneumonitis, bilateral adrenal hemorrhage, and early collapse. Since this patient doubtless succumbed to an overwhelming infection and the Waterhouse-Friderichsen syndrome, it must be taken as an example of the hazard of performing splenectomy during the first year of life.[8] Southard and co-workers [5] mention that their patient became critically ill when bleeding into the respiratory tract was associated with an upper respiratory infection.

Because of lack of uniformity of treatment in the 10 reported cases of this disease, evaluation of therapy is difficult. Prevention of exsanguination by using fresh blood transfusions is an obvious but essential measure. The latter treatment may be particularly helpful in combating hemorrhage if intact platelets are supplied by giving fresh blood which has not come in contact with a wettable surface.[9]

Although Weissman and Tagnon [1] have shown that spontaneous recovery from both the hemangioma and the thrombocytopenia may occur, the severity of the disease in many cases necessitates destruction of the tumor as soon as possible. X-irradiation or radium therapy directed to the tumor site will induce regression of the tumor in most instances, and when it does the thrombocytopenia subsides. Thus irradiation therapy, using superficial treatment with relatively small total dose, appears to be the treatment of choice. So far orthopedic and other serious residuals have not occurred following use of the doses of x-irradiation necessary for treatment of this disease. In contradistinction to the usual criteria, a low platelet count in these patients is not a contraindication to the use of x-ray therapy but instead is a strong indication for continuance or extension of this method of treatment. In these patients the leucocyte counts and bone-marrow aspiration should be the basis for evaluation of the effect of irradiation on the blood-forming tissue.

In our cases the x-ray field sizes were initially large because of the difficulty experienced in locating the tumor boundaries. The massive hemorrhage and brawny edema engulfing and surrounding the essential lesion tended to obscure its limits. Following the initial response to treatment the sites of the tumors were more easily discernible and roentgen therapy was administered more definitively. Whether in other instances a higher dosage of superficial x-ray therapy, more penetrating roentgen therapy, or surgery needs to be used probably will depend upon the location of the tumor, its sensitivity to x-rays, and the severity of the clinical condition. In our second case (C. L. F.) hemorrhage into the tumor occurred twice even after the platelet count had increased to normal levels. Prior to this, bleeding had been so severe and incapacitating that amputation of the extremity was considered by the responsible physicians. It is of interest that for several years following surgical removal of almost all of the hemangioma, the patient experienced minor episodes of hemorrhage into residual tumor sites. Although one cannot ascertain whether or not this patient could have been cured by x-ray treatment alone, surgical removal of the tumor following initial irradiation has given a satisfactory clinical result. A prompt response to x-ray therapy alone was observed in our third patient.

Treatment with high doses of x-ray resulted in prompt regression of the tumor and rapid increase in platelet count in the patient reported by Southard and co-workers,[5] but because of the location of the tumors, intense irradiation therapy of this type could not have been applied to our patients without danger of serious sequelae.

The subsidence of the thrombocytopenia associated with subsidence of the hemangioma in our cases as well as those reported by others speaks eloquently for the concept that the two phenomena are intimately related. However, more directly relating the

hemangioma to the thrombocytopenia is our finding that platelet thrombi were present in sections of the tumors obtained at biopsy, surgery, and necropsy in these cases. The occurrence of large numbers of platelets, as identified by characteristic morphology after Wright's stain, suggests that sequestration, utilization, and destruction of platelets is occurring within the tumor, a possibility originally suggested by Southard and coworkers.[5] Since the association of hemangiomas and thrombopenia has thus far been limited to infants, it seems possible that an increased demand for platelets, reflecting their deposition and sequestration within the tumor, cannot be met by the limited hematopoietic reserves of these young children.

The basis for platelet thrombosis within the tumor is not clear. It may occur secondary to endothelial damage caused by an insufficient blood supply to the growing vessels; it may be a function of altered metabolism (e. g., aerobic glycolysis) of the endothelium associated with rapid proliferation,* or, teleologically speaking, it may even represent an attempt by the host to destroy the tumor by producing vascular occlusion within it. Whatever its basis it appears from microscopic study that the demand for platelets is great. In many of the sections the process is reminiscent of that observed in thrombotic thrombocytopenic purpura. Unlike patients with the latter disease, our cases showed evidence of thromboses only in the hemangioma.

The similarity of the thrombopenic purpura occurring in this disorder and that of chronic idiopathic thrombocytopenic purpura is remarkable. The degree of platelet reduction, chronicity of the disease, and bone-marrow morphology are similar if not identical in the two diseases. Although the significance of this similarity is not entirely clear, the observation is stimulating. Removal of the spleen, the apparent site of platelet destruction, brings dramatic improvement in many cases of chronic essential thrombopenic purpura, but splenectomy has no effect on the platelet count in patients with the thrombopenia - hemangioma syndrome. On the other hand, removal of an apparent site of platelet sequestration in the latter disease brings about an increase in platelet count and return of the bone marrow to normal.

In both disorders bone-marrow studies reveal increased numbers of megakaryocytes which show a shift to the left and little evidence of platelet formation—the so-called megakaryocyte arrest of Dameshek. The significance and nature of megakaryocytic morphology is not entirely clear in either disease. In the cases of thrombopenic purpura due to the presence in the blood of an antiplatelet gamma globulin,† increased platelet destruction is associated with the same megakaryocytic abnormality as is seen in our patients in whom excessive utilization of platelets appears to be associated with the occurrence of platelet thromboses within the vascular tumor. It seems possible that the left shift of megakaryocytes featuring both diseases does not represent a true "arrest" of the megakaryocytes, as many have thought, but rather reflects an increased delivery of platelets to the circulation and failure of the accumulating megakaryocytes to meet the continuing demand.

Another possibility deserves attention, namely, that the megakaryocytic morphology in both forms of thrombopenia does, indeed, represent a developmental arrest induced by a still undiscovered homeostatic regulator set in operation by excessive sequestration of platelets. In essential thrombocytopenia caused by immunological injury to platelets, the sequestration occurs largely in the spleen, while in the hemangioma-thrombopenia syndrome the major site of platelet destruction is the vascular tumor. Removal of the major site of platelet sequestration might result in a resetting of this homeostatic regulator, thus relieving the megakaryocytic arrest and permitting platelet production. This latter hypothesis would explain response to splenectomy in essential thrombopenia, the ineffec-

* References 10 and 11.

† References 12-14.

tiveness of splenectomy in thrombopenia-hemangioma syndrome, and the response of thrombopenia following destruction or regression of the hemangioma in patients with the latter disease. It seems possible that the regulator inducing megakaryocytic arrest may be derived from the platelets themselves during their sequestration or destruction in any part of the body and thus represent a negative feed-back mechanism.

SUMMARY AND CONCLUSIONS

Three new cases of thrombocytopenic purpura associated with hemangioma in infancy are reported, and previous experience with the thrombopenia-hemangioma syndrome is reviewed.

The occurrence in these cases of increased numbers of megakaryocytes, a left shift of the megakaryocytes, and "megakaryocytic arrest" similar to that seen in essential thrombopenic purpura is described.

The occurence of platelet-thromboses within the vessels of the hemangioma is reported, and the suggestion that sequestration of platelets within the tumor accounts for the thrombopenic purpura is made.

In our own cases and those thus far reported it was observed that elimination or destruction of the hemangioma was associated with return of the platelet count to normal, while splenectomy was without effect on the blood dyscrasia.

On the basis of these observations it is postulated that the thrombopenia and hemangioma are intimately related phenomena in these patients.

Hypotheses to explain the relationship are presented.

REFERENCES

1. Weissman, J., and Tagnon, H. J.: Syndrome of Hemangioma and Thrombocytopenic Purpura in Infants, A. M. A. Arch. Int. Med. **92**:523, 1953.

2. Kasabach, H. H., and Merritt, K. K.: Capillary Hemangioma with Extensive Purpura: Report of a Case, Am. J. Dis. Child. **59**:1063, 1940.

3. Rhodes, A. W., and Borrelli, F. J.: Giant Hemangio-Endothelioma with Thrombocytopenic Purpura: Results of Roentgen Therapy, Am. J. Roentgenol. **52**:323, 1944.

4. Silver, H. K.; Aggeler, P. M., and Crane, J. T.: Hemangioma (Capillary and Cavernous) with Thrombopenic Purpura: Report of Case with Observations at Autopsy, Am. J. Dis. Child. **76**:513, 1948.

5. Southard, S. C.; DeSanctis, A. G., and Waldron, R. J.: Hemangioma Associated with Thrombocytopenic Purpura: Report of Case and Review of Literature, J. Pediat. **38**:732, 1951.

6. Bogin, M., and Thurmond, J.: Hemangioma with Purpura, Thrombocytopenia and Erythrocytopenia, A. M. A. Am. J. Dis. Child. **81**:675, 1951.

7. Dameshek, W., and Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura, a Form of Hypersplenism, Blood **1**:27, 1946.

8. King, H., and Shumacker, H. B., Jr.: Splenic Studies: I. Susceptibility to Infection After Splenectomy Performed in Infancy, Ann. Surg. **136**:239, 1952.

9. Hirsch, E. O.; Farre-Gilly, J., and Dameshek, W.: Thrombopathic Thrombocytopenia: Successful Transfusion of Platelets, Blood **5**:568, 1950.

10. Thomas, L., and Stetson, C. A., Jr.: Studies on the Mechanism of the Shwartzman Phenomenon, J. Exper. Med. **89**:461, 1949.

11. Stetson, C. A., and Good, R. A.: Studies on the Mechanism of the Shwartzman Phenomenon: Evidence for the Participation of Polymorphonuclear Leucocytes in the Phenomenon, J. Exper. Med. **93**:49, 1951.

12. Harrington, W. J.; Minnich, V.; Hollingsworth, J. W., and Moore, C. V.: Demonstration of the Thrombocytopenic Factor in Blood of Patients with Thrombocytopenic Purpura, J. Lab. & Clin. Med. **38**:1, 1951.

13. Sprague, C. C.; Harrington, W. J.; Lange, R. D., and Shapleigh, J. B.: Platelet Transfusions and Pathogenesis of Idiopathic Thrombocytopenic Purpura, J. A. M. A. **150**:1193, 1952.

Salmonella sp. (Type Montevideo) Osteomyelitis

Report of a Case and Review of the Literature

N. C. ELLENBOGEN, M.D.
JEROME RAIM, M.D.
and
L. GROSSMAN, M.D., Miami, Fla.

This case report is presented because of its rarity, the extensive osteomyelitic lesion, and the difficulty encountered in establishing the diagnosis early in the disease.

REPORT OF CASE

S. F., a 27-month-old Negro boy, was admitted to Jackson Memorial Hospital on Sept. 14, 1954, with the chief complaint of fever and swelling of the right elbow of three days' duration.

The patient was first seen at Jackson Memorial Hospital seven days prior to admission, with a two-day history of fever and intermittent pain in all four extremities. Examination at this time revealed a well-developed, well-nourished, Negro boy, having a rectal temperature of 99 F and no significant physical findings. Laboratory studies showed a hemoglobin of 9.4 gm. per 100 cc. (capillary blood) and 12 nucleated RBC's per 100 RBC's, and the sickling preparation demonstrated 85% sickling. The diagnosis of sickle-cell crisis was made, and the patient was treated symptomatically. He returned the following day because of persistent symptoms. Physical examination now revealed rectal temperature 102.6 F and marked injection of the tonsils and posterior pharynx. No other abnormal physical findings were present. Laboratory data showed a hemoglobin of 7.4 gm. per 100 cc. (capillary blood). He was treated with 300,000 units of penicillin procaine and acetylsalicylic acid. Two days later he was seen by a private physician, who withdrew blood from the right antecubital space. The child was then treated with penicillin and an unknown oral medication. On Sept. 11, 1954, six days after the onset of the first symptoms of joint pains and three days prior to hospitalization, the mother noted swelling of the right elbow, and the child was not able to move this arm without severe pain. The pain, swelling, and fever were progressive. Two days prior to admission the patient had three watery stools.

Past history presented the fact that one year before admission a diagnosis of anemia was made at another hospital and the child was treated with blood transfusions. No other pertinent history was obtained.

The physical examination at the time of admission revealed a rectal temperature of 102 F, pulse 112 and regular, respirations 20. The child was well developed, well nourished, and quite irritable. He held his right arm flexed against his body with his left hand and resisted manipulation. There was marked swelling of the right arm from midforearm to midhumerus. The swelling was located anteriorly, above and below the antecubital space, but the antecubital space and the posterior surface of the arm were not involved. These swollen areas were warm, extremely tender, and nonfluctuant. The remainder of the physical examination was entirely within normal limits.

Laboratory studies on admission: hemoglobin 6.5 gm. per 100 cc.; RBC's 2,680,000, with 48 nucleated RBC's per 100 RBC's; WBC 18,950, with nucleated RBC correction 12,710. Differential: 6% stab cells, 38% segmented neutrophiles, 55% lymphocytes, and 1% monocytes. Sickle-cell preparation revealed 25% sickling. Routine urinalysis was normal except for 5-10 RBC's per high-power field. Serological test for syphilis was negative. Roentgenographic study of the right elbow showed soft-tissue swelling but no evidence of bone involvement.

Hospital Course.—On admission a blood culture was drawn, and the patient was started on 300,000 units of penicillin procaine per day. The patient ran a septic course, with remittent temperatures recorded as high as 105 F rectally. On the third hospital day the arm remained swollen and warm

Submitted for publication May 13, 1955.

From the Department of Pediatrics of the University of Miami School of Medicine and the Pediatric Service of the Jackson Memorial Hospital.

but seemed somewhat less tender. The antibiotic was changed to 40 mg. of intramuscular oxytetracycline every eight hours and 0.5 gm. of streptomycin every six hours. Spinal-fluid examination was normal. Another blood culture was drawn. Blood studies now showed the following: hemoglobin 4.1 gm. per 100 cc.; 2,600,000 RBC's; WBC's corrected to 18,000. The serum bilirubin was 0.25 mg. per 100 cc. direct, total 0.65 mg. per 100 cc. Roentgenographs of the chest were obtained and revealed a right-lower-lobe pneumonia with possible extension to the right upper lobe. The temperature remained elevated and fluctuated between 104 and 106 F. The patient was transfused with 250 ml. of whole blood on two successive days. The blood culture drawn on the third hospital day was reported growing an organism culturally resembling a Salmonella and serologically testing for Salmonella Group C. The admission blood culture and that obtained on the second hospital day showed no growth.

Sensitivity studies of this organism as determined by the disc method were as follows:

Tetracycline	sensitive
Oxytetracycline	sensitive
Streptomycin	resistant
Polymyxin	resistant
Chloramphenicol	resistant

Agglutination studies obtained on the 10th hospital day for typhoid "O" antibody were negative and for "H" antibody, 1:40. Paratyphoid A agglutinations were negative, and Paratyphoid B were 1:320.

Fig. 1.—Right arm, 15th hospital day.

Fig. 2.—Forty-fifth hospital day.

Stool and urine cultures were repeatedly negative for growth of Salmonella organisms. The septic course continued. Roentgenographic examination of the chest on the 14th hospital day revealed bilateral consolidation of a patchy nature with a partial atelectasis of the right middle lobe.

Clinically there continued to be moderate improvement of the right arm, with increased motion and decreased swelling. A second roentgenographic examination of the right arm, on the 15th hospital day, revealed that the diaphyses of the humerus and radius were involved by a process giving them a "moth-eaten" appearance (Fig. 1). A complete skeletal survey at this time showed no other osteolytic lesions. Blood cultures obtained at this time were later reported as showing no growth. On the 15th hospital day the antibiotic was changed to chloramphenicol palmitate, 375 mg. every six hours, because of the continued septic course and the limitations of the disc method of determining sensitivity. On the 16th hospital day a bone marrow aspiration and culture were obtained. The cellular study was normal, but the culture was positive for Salmonella sp. (Type Montevideo). On the 20th hospital day, five days after chloramphenicol was begun, the temperature returned to normal and remained so thereafter. On the 28th hospital day the chloramphenicol was decreased to 250 mg. every six hours after 14 days at the previous dosage.

Slowly the swelling decreased and motion returned, so that by the 30th hospital day the patient was clinically well, and roentgenographic study obtained on this day revealed an involucrum over the radius and humerus. On the 35th hospital day the chloramphenicol therapy was discontinued. On the 45th hospital day the involucrum was reported as being larger and the external border indistinct, suggesting a healing process of osteomyelitis (Fig. 2). At no time was fluctuation of the right arm noted. The patient was discharged improved on the 47th hospital day.

REVIEW OF THE LITERATURE

There are over 150 species of Salmonella organisms harbored in the intestinal tracts of man and animals. Infections caused by these organisms, with their innumerable means of spread, still remain a major health problem despite improved methods of sanitation, food inspection, and therapy. The over-all mortality from Salmonella infections in a series of 2000 cases, exclusive of S. typhosa, was 5.1%.*

* References 1 and 2.

Clinical manifestations of disease processes caused by the Salmonella organisms are many and varied. As a means of simplification, Bornstein has classified the clinical picture into three syndrome groupings, namely, Salmonella fever, Salmonella septicemia, and Salmonella gastroenteritis. A fourth group, a pulmonary type, had been proposed, but bronchopneumonia may be a part of Salmonella fever, just as lung abscesses and other purulent pulmonary processes may be a manifestation of Salmonella septicemia. Any one clinical type may develop the symptom-complex of the others. The outcome of the disease and the success of treatment are more dependent on the clinical syndrome than upon the causative organism.[8]

The clinical course of Salmonella fever is characterized by fever and malaise, usually lasting from one to three weeks. Leucopenia may be present. A slow pulse rate is not constant. Abdominal pain may simulate an acute surgical abdomen. Bronchitis and bronchopneumonia may occur. Stool cultures may

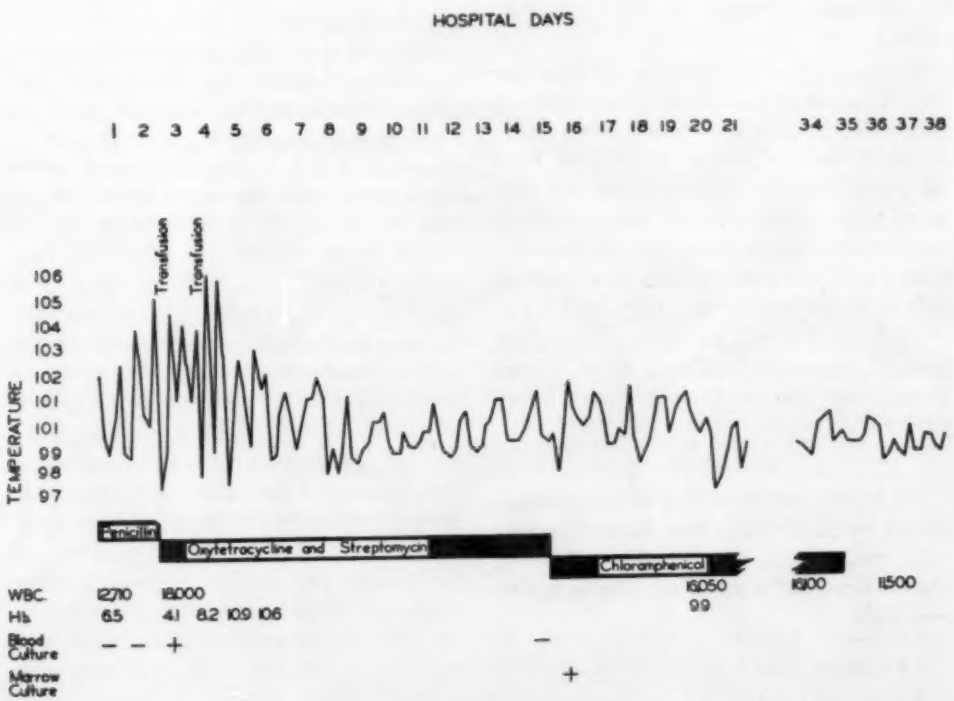


Fig. 3.—Hospital course of patient.

remain negative for weeks, and bacteria may be found in the urine. Blood cultures are often positive early in the disease, and positive cultures are more commonly obtained from the bone marrow than from the blood. The septicemic type is characterized chiefly by high remittent fever and positive blood cultures. Salmonella gastroenteritis usually has a period of incubation from 3 to 24 hours. The disease may be acute or subacute. In the acute form vomiting is commonly the first symptom and diarrhea is frequent. The subacute form is characterized by prolonged course of mild gastrointestinal symptoms. The tendency for septic complications is especially marked in the newborn baby.[3] In a series of 1497 cases of Salmonella infections reported by Seligmann from The New York Salmonella Center, 17% were in infants, 40% were in children under 10 years of age.[2]

Osteomyelitis and arthritis may occur. In children under 2 years of age, as many as 20% of S. choleraesuis infections present these manifestations.† Injury in the osteomyelitis is considered to be important, but the duration of time for its localization varies.‡

The pathogenic organism in the case history reported is one of the rarer types of Salmonella, S. sp. (Type Montevideo). This organism was first isolated in Uruguay from the lymph nodes of healthy swine and later found to be associated with certain cases of summer diarrhea in infants.§ Its incidence is very low, being only 0.13% in a series of 1075 cases in Mexico [9] and 0.2% in a series of 2916 cases in this country.[2] There have been 17 known outbreaks of S. sp. (Type Montevideo) in the United States before 1947.[10]

COMMENT

We have presented a case of salmonellosis caused by a relatively rare type of Salmonella organism, S. sp. (Type Montevideo). Our patient had a remittent febrile course, and the gastrointestinal symptoms were minimal. The illness was of the septicemic type, according to Bornstein's classification.[3] Seligmann, in a series of 78 cases of S. sp. (Type Montevideo), reported only 1 septicemic type.[2]

Organisms were obtained from the patient's peripheral blood and bone marrow, but stool and urine cultures failed to demonstrate the pathogen. In Seligmann's series, although the reporting was not complete, only two had positive blood cultures.[2] The value of repeated blood cultures, even while receiving antibiotics, is borne out, as positive cultures were obtained while our patient was receiving antibiotic therapy.

With the presence of sickling, the child was treated early in the course of his illness, symptomatically, for sickle-cell crisis. Though this combination of circumstances is no doubt unusual, it made the diagnosis of the septicemic type of salmonellosis even more difficult.

The significance of the trauma of needle puncture or the pressure used in holding the arm in the localization of the osteomyelitis can only be speculated upon.

Although sensitivity studies as determined by the disc method did not indicate that chloramphenicol was the antibiotic of choice, clinically with the institution of this therapy the patient began to improve. Actual recovery, however, may have been due to the patient developing his own immunity and/or the use of chloramphenicol. Satisfactory response was not noted with oxytetracycline, streptomycin, or penicillin. The unpredictable response of this Salmonella organism to antibiotics conforms with other reported therapeutic responses.[11] Kunstader, in a report of 10 patients with Salmonella infection, stated that of five treated with chloramphenicol, three responded favorably. One patient who did not respond to chloramphenicol or streptomycin responded to oxytetracycline, and one patient who did not respond to chloramphenicol alone responded to chloramphenicol plus oxytetracycline. Four cases were successfully treated with oxytetracycline alone.[11]

† References 3 and 4.

‡ References 5 and 6.

§ References 7 and 8.

SUMMARY

A case of Salmonella sp. (Type Montevideo) infection manifesting symptoms of septicemia resulting in osteomyelitis and bronchopneumonia is presented. The difficulty of early diagnosis, the possible role of trauma in the location of the osteomyelitis, and the value of repeated blood and bone marrow cultures, even during antibiotic therapy, as well as the unpredictable response to therapy are discussed.

REFERENCES

1. Zinsser, H.: Zinsser's Textbook of Bacteriology, revised by D. T. Sinuth and others, Ed. 9, New York, Appelton-Century Crofts Inc., 1948, pp. 443-475.

2. Seligmann, E.; Saphra, I., and Wassermann, M.: Salmonella Infections in the U. S. A., J. Immunol. **4**:69, 1946.

3. Bornstein, S.: State of the Salmonella Problem, J. Immunol. **46**:439, 1943.

4. Harvey, A. M.: Salmonella Suipestifer Infection in Human Beings, Arch. Int. Med. **59**: 118, 1937.

5. Miller, A. A.: Salmonella Dublin Osteomyelitis of the Spine, Brit. M. J. **1**:194, 1954.

6. Guerrier, H. P., and Greenburgh, H.: Salmonella Choleræsuis Osteomyelitis, Brit. J. Surg. **41**:457, 1954.

7. Hormaeche, E., and Salsamendi, R.: Sobre la presencia de salmonelas en los ganglios mesentéricos de cerdos normales, Arch. urug. med. **9**: 665, 1936.

8. Myers, W. A., and Eckles, L. E.: Epidemic of Food Infection Caused by Salmonella Montivideo, U. S. Nav. M. Bull. **43**:1067, 1944.

9. Varela, G., and Olarte, J.: Classification and Distribution of 1,075 Cultures of Salmonella Isolated in the City of Mexico, J. Lab. & Clin. Med. **40**:73, 1952.

10. Vinke, T. H., and Downing, H. F.: Salmonella Infection Involving the Knee Joint, J. Bone & Joint Surg. **29**:232, 1946.

11. Kunstadter, R. H.; Milzer, A., and Kagan, B. M.: Chloramphenicol and Terramycin in the Treatment of Salmonella and Shigella Infections, J. Pediat. **39**:687, 1951.

News and Comment

ANNOUNCEMENTS

Institutes in Care of Premature Infants.—The Institutes for Physicians and Nurses in the Care of Premature Infants at The New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, are currently in their seventh year of operation. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses of four weeks' duration. Participants pay no tuition fee, and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the 1955-1956 year are definitely scheduled to start on the following dates: Sept. 26, 1955; Nov. 21, 1955; Jan. 30, 1956. In addition, if the number of applicants is sufficient to warrant it fourth and fifth Institutes will be scheduled beginning April 2, 1956, and May 21, 1956. Early application for these Institutes is essential, since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 E. 68th St., New York 21.

Treatment of Streptococcal Carrier State in a Rural School

THOMAS B. HILL, M.D., Lowell, Mich.

The successful use of oral penicillin to interrupt hemolytic streptococcal epidemics in large groups of armed forces is well established.[1] This study is an attempt to apply the principles of group antibiotic therapy to prevent recurrent hemolytic Streptococcus infections in rural areas.

PROBLEM

For a two-year period, members of eight families had repeated upper-respiratory infections from which pharyngeal or tonsillar cultures were positive for a hemolytic Streptococcus (grouping and typing were not done). Penicillin therapy in the form of 200,000 units of an oral buffered penicillin three times a day for a period of 7 to 10 days or later 1,200,000 units of benzathine penicillin G (Bicillin) intramuscularly would give clinical cure of these infections, but the repeated recurrences made it evident that either a bacteriological cure was not obtained or reinfection was taking place. Cultures of other members of the family were usually negative, but even when they were positive and the carriers were adequately treated there was no apparent decrease in the rate of recurrence when protection of the penicillin was removed. The possibility of reinfection from house dust was considered, but no practical follow-up of this source was available. Attention was then centered upon the country school to which the children of the eight families went. In the school year of 1953-1954 there had been a scarlet fever epidemic and repeated absences of children from school for sore throats and ear infections. Approximately 65 children attended school, with classes up to the eighth grade held in two rooms. When clinical hemolytic Streptococcus infections began to recur in several of the families with the opening of school in September, 1954, the Mothers' Club of the school accepted the recommendation to apply the principles of group treatment to prevent recurrences if the throat cultures of a sufficient number of the children should be positive. The Mothers' Club was willing to buy the necessary penicillin, and the teachers accepted the responsibility of administering it. Permission slips were signed by almost all the parents for the initial throat cultures, although a smaller number cooperated in the other stages.

METHOD

The initial throat cultures of 56 pupils were taken on Nov. 29, 1954. Of these cultures 15, or 27%, were positive for a hemolytic Streptococcus. While arrangements for the treatment were being made, Christmas vacation came close, and it was decided to postpone treatment until after the 10-day vacation period, to determine if the separation of the pupils for this period would appreciably affect the carrier rate. On Jan. 3, 1955, repeat cultures were taken of 59 pupils, and 16, or 27%, were again positive.

The following treatment was carried out: A tablet containing 200,000 units of oral buffered penicillin was given to each child at about 10:30 a. m. and another at 3:00 p, m. The kindergarten pupils took the pills home with them and were to take them at least two hours after lunch. This program was followed for the five school days of the week, being interrupted by the week ends, for a total of 13 treatment days. A total of 51 pupils started the schedule

Submitted for publication July 15, 1955.

The laboratory work for this study was done by the Grand Rapids Branch of the Michigan Department of Health Laboratories.

on Jan. 3, 1955, but 4 of these interrupted for the following reasons: One boy developed angioneurotic edema and hives after 1 week and finished the treatment with 0.3 gm. of sulfadiazine twice daily; one girl had nausea after the first two doses and refused further medication; one boy developed fever on the 9th day of treatment and discontinued, and one girl had a very sore mouth and discontinued on the 10th day. Four additional children received several doses of intramuscular penicillin from their private physicians, and two had tonsillectomy and adenoidectomy, one of these taking the course of oral penicillin up to the time of the operation. Three children had received penicillin therapy in the four weeks prior to Jan. 3 and did not take the group therapy. A total of 58 pupils, or 88%, of the 66 then in attendence at the school took some form of treatment directed at reducing the carrier state.

Cultures were repeated Jan. 26, 1955, six days after completion of penicillin therapy, on 56 pupils, and only 3, or 5%, of these were positive. One of these three had no treatment; one had interrupted on the 9th day because of fever; and only one had completed the 13 days of treatment.

Cultures were again repeated three months later, on April 26, 1955, on 64 pupils, with 8, or 12%, positive reports. The carrier rate was again increasing, but there was not one clinical Streptococcus infection seen during these three months by me in the eight families where previous recurrent infections had given the reason for study and treatment.

The goal of the study was to determine if oral penicillin therapy given in doses less than those considered adequate for treatment of clinical hemolytic Streptococcus infections could adequately lower the carrier rate in a rural school so that the frequency of clinical Streptococcus infections could be decreased. This was successfully demonstrated, but, in addition, several other interesting observations were made.

All children with positive cultures still had their tonsils and adenoids present, although 18 out of the 70 children that at one time or another participated in the study (the number of pupils in attendance fluctuated as families moved) had had previous tonsillectomy and adenoidectomy. Whether this would have been true with carefully taken nasopharyngeal swabs instead of the quick oral swab taken in a gagging youngster would be important in considering whether tonsillectomy and adenoidectomy would be an adequate means of treating a chronic carrier. The actual carrier rate might have been significantly higher if both nose and throat swabs had been taken.

The gradually rising carrier rate three months after the completion of therapy was occurring entirely among the same children who had been chronic carriers previously. Possibly these children were being reinfected within their own families from the adults and children not attending this school, or possibly true bacteriological cure had not been obtained at the time of the third culture but Streptococcus colonies had been reduced to such a small number that they were not obtained by the throat swab.

Results of Throat Cultures Before and After Penicillin Therapy, Listing Only Those Showing at Least One Positive Hemolytic Streptococcus Culture

Pupil	Culture, 11/29/54	Culture, 1/3/55	Penicillin Therapy	Culture, 1/26/55	Culture, 4/26/55
E. B.	+	0	Yes	0	0
A. H.	0	+	Yes	0	+
E. H.	0	+	Yes	0	+
F. H.	+	0	Yes *	0	0
L. H.	+	0	No †	..	0
P. K.	+	+	Yes	..	0
S. M.	+	+	Yes	0	0
B. P.	..	+	Yes	+	+
R. S.	+	+	Yes	..	+
T. S.	+	0	Yes ‡	+	0
T. S.	..	+	No	0	+
D. S.	+	+	Yes	..	+
F. S.	..	+	No	+	+
D. T.	+	+	Yes	0	0
S. T.	+	0	Yes §	0	0
E. V.	+	+	Yes	0	+
G. V.	+	+	Yes	0	0
F. V.	+	+	Yes	0	0
D. V.	..	+	Yes ‖	0	0
J. V.	+	+	Yes	0	0
R. V.	0	+	Yes	0	0
M. W.	+	0	Yes	0	0

* Had tonsillectomy and adenoidectomy after 2 wk. oral penicillin.
† Had tonsillectomy and adenoidectomy.
‡ Discontinued on 9th day because of fever.
§ Penicillin I.M. by private physician.
‖ Developed angioneurotic edema on 5th day, took sulfadiazine, 0.3 gm. b.i.d. for next 8 days.

A number of hemolytic Staphylococcus infections were recorded, with 7 out of 56 on the first cultures and 2 out of 56 and 3 out of 64 on the third and fourth cultures. Cultures were taken from two of the children who developed fever and sore throats during the

treatment period and were negative for hemolytic Staphylococcus. The penicillin therapy apparently reduced or at least did not adversely affect the carrier state for hemolytic Staphylococcus.

The total number of side-reactions reported was higher than that usually reported, but only the one case of angioneurotic edema could be considered a significant reaction. Inasmuch as many of the children had to chew the tablets before swallowing them, one would expect some sore mouths and lips. The two cases of fever may or may not have been related to the penicillin therapy, although one subsided rapidly on discontinuance of penicillin and the other on addition of erythromycin without discontinuing the penicillin.

The Table shows only those pupils in the school who had at least one positive culture during the course of the study. As stated before, all of these pupils had their tonsils and adenoids at the start of the study.

SUMMARY

Constantly recurring clinical hemolytic Streptococcus infections in eight families were traced to the rural school serving these families. A Streptococcus carrier rate of 27% among the pupils was reduced to 5% by oral penicillin therapy given to the majority of the pupils over a thirteen-day period. The reduction in the carrier rate was coincident with no further clinical infections in the families under the author's medical care.

REFERENCE

1. Bernstein, S. H.; Feldman, H. A.; Harper, O. F., Jr., and Klingensmith, W. H.: Mass Oral Penicillin Prophylaxis in Control of Streptococcal Disease, A. M. A. Arch. Int. Med. **93**:894-898 (June) 1954.

News and Comment

ANNOUNCEMENTS

Residency in Pediatric Oncology.—Applications for the residency from July 1, 1956, to June 30, 1957, in Pediatric Oncology at Memorial Center for Cancer and Allied Diseases in New York will be received up to Nov. 1, 1955. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3600 annually plus maintenance. For application forms and information write Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21.

Seventh Annual Maurice Lamm Blatt Memorial Fund Lecture.—The Pediatric Staff of the Cook County Hospital announces that the Seventh Annual Maurice Lamm Blatt Memorial Fund lecture will be given Monday, Oct. 24, 1955. Dr. Wolf W. Zuelzer, Director of Laboratories of the Children's Hospital of Michigan, will speak on "Maternal Fetal Incompatibility in the O-A-B-System and Hemolytic Disease of the Newborn." The lecture will be presented at 8:30 p. m. in the medical amphitheatre of the Cook County Hospital.

Fellowship in Pediatric Neurology.—A Fellowship in Pediatric Neurology is available at the Cook County Children's Hospital, in Chicago. The Fellowship will provide clinical training in the diagnosis and rehabilitation of children with neuromuscular handicaps. In addition, the trainee will be expected to participate in a clinical laboratory problem. The annual stipend will vary from $3000 to $5000, depending upon the qualifications of the applicant.

For further information write M. A. Perlstein, M.D., 4743 N. Drake Ave., Chicago 25.

CORRECTION

In the article "Ulcerative Colitis in Children: Observations in Selected Patients," by Drs. Joseph B. Kirsner, Howard F. Raskin, and Walter L. Palmer (August issue, p. 141), the last complete sentence in the left-hand column of page 147 should read: "There was a 71% disappearance of Congo red dye from the serum."

The Epidemiological Retreat of Tuberculosis

A Ten-Year Survey of Tuberculin Reactors at a Children's Dispensary

KARL E. KASSOWITZ, M.D., Milwaukee

The epidemiological retreat of tuberculosis in the United States during the last quarter of a century presents a public health phenomenon of considerable complexity. In most other infectious diseases the success of preventive medicine has been due chiefly to the application of two principles: elimination of sources of infection and active immunization. In tuberculosis, on the other hand, a combination of several circumstances has resulted in the spectacular decline of morbidity and mortality. The most important factors are (1) elimination of bovine tuberculosis by way of compulsory tuberculin testing of cattle, (2) improvement in the standard of living and particularly housing, (3) more accurate case-finding procedures including routine standard and microfilm x-rays, (4) tuberculin testing, (5) bacteriological conversion by chemotherapy of large numbers of formerly intractable cases, and (6) BCG vaccination of potential contacts.

One of the most revealing and time-honored yardsticks by which we are able to measure the low-water mark of endemic tuberculosis in a community is the tuberculin test. Yet there are preciously few city or county health departments that will be ready to venture more than a rough estimate as to the perecentage of positive reactors at school age.

There are some reports of widely scattered tuberculin surveys available over a period of years rather than a continuous statistical assessment of the declining curve of the number of positive reactors. Before reporting on our own results we may look at the percentages of reactors as published in previous surveys without going too far afield into the historic times and places of tuberculosis pandemics abroad.

Chadwick and Zacks [1] found 28% positive reactors in a series of New England school children tested in 1929. However, they mention a city of 60,000 where the number of children reacting varied from 11% to 60%, according to different school districts.

In a widely quoted program of tuberculin testing in Chicago schools during a three-year period from 1938 to 1940, Tice [2] discovered 27,401 reactors out of a total of 167,345 children, which is a percentage of 16.37. The breakdown according to age and type of schools appears quite significant. Public school, elementary grades 12.82%, high school 21.34% reactors; Catholic school, elementary grades 12.39%, high school 20.96%; Lutheran school, elementary grades 10.28%; other private high schools, 30.43%.

If we skip from these "ancient" times to more recent surveys we find, for instance, the following figures among primary school children in Sidney, Australia [3]: in an inner industrial area 7.3%, in an outer suburban residential area 4.1%, among migrant children 15% positive reactors. Pleyte and coworkers [4] found 5.3% reactors among 27,905 Wisconsin children and juveniles up to 18 years. Very recently Gray,[5] using the patch test, reported 4.2% reactors among 15,755 St. Louis County school children.

As to our particular survey of positive reactors to tuberculin, there are some significant differences between the above-quoted

Submitted for publication June 29, 1955.

From the Outpatient Department of Milwaukee Children's Hospital. Associate Clinical Professor of Pediatrics, Marquette University.

material, which presents more or less a cross section of school populations, and our outpatient department cases. This being strictly a free clinic, the eligibility for admission being supervised by the social service department, it definitely serves the lower socioeconomic strata of the county population, including a considerable number of Negroes, Mexicans, Puerto Ricans, recent immigrants from Europe, and what the Australian author terms migrant children.

Another important difference in our material is that, far from being a cross section of the population of Milwaukee County, it presents a selection of cases in the age group of 3 to 16 years which from the medical point of view offered some suspicion of underlying tuberculosis. The specific leads toward suspected active disease are, of course, quite numerous, if vague. They are, in the main, history of possible family contact, history of repeated or persistent "chest colds," malnutrition, cervical lymphadenopathy, questionable and persistent chest x-ray lesions, questionable extrapulmonary inflammatory or degenerative processes, like bone and joint lesions, and, finally, unaccounted for acceleration of the blood sedimentation rate.

Percentages of Positive Tuberculin Reactors

Year	Total Census of New Outpatients	Total No. Tuberculin Tested	No. Positive Reactors	Per Cent Tuberculin Reactors
1944-1945	1,450	873	37	4.3
1945-1946	2,384	876	41	4.7
1946-1947	2,245	770	23	3.0
1947-1948	2,425	802	37	4.7
1948-1949	2,389	932	28	3.0
1949-1950	2,270	1,003	31	3.0
1950-1951	2,008	864	30	3.5
1951-1952	2,175	999	30	3.0
1952-1953	2,165	789	26	3.3
1953-1954	2,493	596	22	3.5

Therefore, the number of 8506 cases tested over a 10-year period out of a total census of 22,004 outpatients does not actually compare with the above-quoted average figures among what has to be considered normal children. For this very reason the surprisingly low number of our positive reactors as reported below appears that much more significant.

The testing technique consisted of the standard intracutaneous Mantoux method with the following provisos: the dilution of old tuberculin applied primarily was either 1:10,000 or 1:1000, but no case was ever entered as negative unless tested or retested with the 1:1000 dilution. The practice of injecting 0.2 cc. instead of 0.1 cc. appeared to us as an added safeguard against false-negative reactions due to insufficient depots of reactor fluid or to leakage.

Our Table shows the number of "tuberculosis suspects" tested out of the total figure of outpatients per year and the number and percentage of reactors.

COMMENT

Although our case material does not constitute what could be considered an average representation of the children's population of Milwaukee County and not even a cross section of the lower social strata, the results of our tuberculin testing of tuberculosis suspects yielded some of the lowest percentages of positive reactors on record for an industrial city of this size.

It can be deduced that long before the advent of specific antibacterial therapy and without the use of any method of active immunization (BCG), communities like ours had to a great extent succeeded in reducing and eliminating sources of infection among adults.

However, in comparing the average percentage of reactors of the years 1944 to 1948 with the quinquennium 1949 to 1954, we still see a decline from 3.92% to 3.26%.

It seems fairly obvious that the children selected for testing on account of vague clinical suspicion of underlying tuberculosis did not yield a much higher number of positives than would have any other average group of the same ages. This apparently is due to the fact that the symptomatolgy, the physical findings, and even the radiological manifestations of tuberculosis in children are so obscure and uncharacteristic that the tuberculin

test constitutes practically the only conclusive proof of the infection being present.

SUMMARY

A tuberculin testing program of 8506 outpatients between 3 and 16 years of age who were considered tuberculosis suspects yielded only 304 positive reactors, which is a surprisingly low percentage of 3.5.

A breakdown for the last 10 years shows a steady, if somewhat irregular, decline per year from a maximum of 4.7% to a minimum of 3% reactors, the average for the years from 1944 to 1948 being 3.92%, compared with 3.26% for the last 5 years.

The credit for this most gratifying epidemiological recession of tuberculosis among Milwaukee children may be attributed to a number of factors, some local, some nationwide; to mention a few: elimination of bovine tuberculosis, improvement in the standard of living and especially housing, efficient case finding and treatment programs, and, thereby, drying up progressively the sources of infection.

REFERENCES

1. Chadwick, H. D., and Zacks, D.: The Incidence of Tuberculous Infection in School Children, New England J. Med. **200**:332 (Feb. 14) 1929.

2. Tice, F.: Tuberculin Testing in the Chicago Schools, Bulletin, City of Chicago Municipal Tuberculosis Sanitarium, 1938-1940, Vols. 18, 19, and 20, pp. 7-92.

3. Mills, R. M.: Tuberculous Infection and Its Source in Primary School Children, M. J. Australia **2**:530 (Oct. 3) 1953.

4. Pleyte, A. A.; Kerwin, D., and Sternitzky, D.: The Value of Tuberculin Skin Testing as a Case-Finding Procedure, Journal-Lancet **73**:130 (April) 1953.

5. Gray, W. C.: Mass Tuberculin Patch Testing of School Children: Preliminary Report of Community Plan, J. A. M. A. **158**:8 (May 7) 1955.

Effect in the Newborn Infant of Reserpine Administered ante Partum

IRWIN S. BUDNICK, M.D.
SANFORD LEIKIN, M.D.
and
LEROY E. HOECK, M.D., Washington, D. C.

Reserpine is a pharmacologically active alkaloid derivative prepared from the roots of Rauwolfia serpetina, a small shrub growing wild in certain regions of India and other tropical countries.[1]

It is a crystalline colorless substance which is insoluble in water and moderately soluble in alcohol. Its empirical formula is $C_{33}H_{40}O_9N_2$.

This drug has several varied pharmacological effects.[2] These consist of hypotension, bradycardia, hypothermia, increase in gastrointestinal motility, myosis, and general tranquilization.[3]

Because of its effect in lowering blood pressure, it is used in certain hypertensive states by itself and in combination with other drugs.* Some of the undesirable effects of this drug in the human are mental depression,[5] diarrhea, and weight gain. Headache, dizziness, and nausea are also reported.[1] Nasal stuffiness or "congestion" in varying percentages has been noted by several authors.† This may be relieved by topical vasoconstrictors and antihistaminics. In the pediatric age group experience with reserpine has been limited.

During the month of June, 1954, several newborn infants in our nursery were noted to have nasal discharge shortly after birth. Because of the age of onset, afebrile course, and lack of symptoms in the mothers it was felt that an infectious process was unlikely, and an investigation was made to determine if possible the etiologic agent. We therefore investigated all cases of nasal discharge occurring during the following three-month period. During that time reserpine, hydralizine (Apresoline) and cryptenamine were being used by the department of obstetrics for the treatment of hypertension associated with toxemia of pregnancy. Meperidine (Demerol) and vinbarbital (Delvinal) were used for their analgesic effects; chlorpromazine and the barbiturates were employed for sedation, and acetazoleamide (Diamox) was used to reduce edema. The above analgesic agents had been used for a considerable period of time by the obstetrical department and had never produced nasal discharge. Furthermore no such reactions have been noted from hydralazine, cryp-

Submitted for publication July 15, 1955.

Reserpine supplied as Serpasil by Ciba Pharmaceutical Products, Inc.

From the Department of Pediatrics, District of Columbia General Hospital. Resident in Pediatrics, District of Columbia General Hospital, and Assistant Clinical Instructor, Georgetown University School of Medicine (Dr. Budnick); Medical Officer in Pediatrics, District of Columbia General Hospital, and Clinical Instructor in Pediatrics, George Washington University School of Medicine (Dr. Leikin); Chief Medical Officer in Pediatrics, District of Columbia General Hospital, and Adjunct Clinical Professor in Pediatrics, Georgetown University and George Washington University Schools of Medicine (Dr. Hoeck).

* References 1-3.

† References 1, 6, and 7.

tenamine, acetazoleamide, chlorpromazine, and the barbiturates. However, it is known that reserpine may produce "nasal congestion" in the adult. Below are a Table and a discussion of the pertinent information of 12 infants in our nursery who had nasal discharge and whose mothers received medication prior to delivery. Only one other infant had nasal discharge during this period. However, in this case the mother received no drugs, and his clinical course was extremely mild, differing greatly from the other 12 infants.

Twelve Newborn Infants Whose Mothers Received Medications Prior to Delivery

Drugs Administered to Mothers				Symptomatology						
	Reserpine									
Cases	Amount, Mg.	Time Before Delivery, Hr.	Other Drugs *	Onset After Birth, Hr.	Duration, Days	Nasal Discharge	Cyanosis	Retraction	Lethargy	Poor Feeding
1	2.5	1	M, V	1	Died 10	X	X	X	X	X
2	2.5	6	M, H	8	3	X	..	X	..	..
3	2.5 2.5	40 21	A, H, Ch, B	27	2	X	..	X	..	..
4	2.5	¼	M, V, Cr	22	1	X	..	X	..	X
5	2.5	11	None	8	3	X	..	X	..	..
6	2.5	2	B	9	1	X	..	X	..	..
7	2.5	2	M, V	12	6	X	..	X	..	X
8	2.5	3	M, V, Cr	6	3	X	..	X	..	..
9	10.0	16	None	12	Died 3	X	X	X	X	X
10	8.0	9	M, V, Cr, B	12	5	X	X	X	X	X
11	2.5 2.5	1 ¼	M, V	21	2	X	..	X	..	..
12	4.0 cc.†	2	Cr	10	5	X	..	X	..	..

* M indicates meperidine (Demerol); V, vinbarbital (Delvinal); H, hydralazine (Apresoline); A, acetazoleamide (Diamox); Ch, chlorpromazine (Thorazine); B, barbiturates; Cr, cryptenamine (Unitensin).

† Dosage in mg. not known.

CLINICAL FINDINGS

These 12 infants were full term. Only two were delivered by Caesarean section. Nasal discharge was the earliest and most prominent sign. The discharge varied from a slight watery to a somewhat mucoid material and never appeared purulent. The mucosal lining never appeared inflamed. The absence of mouth breathing in the newborn infant made the obstructive characteristics of this discharge impressive, although the quantity of drainage was not profuse. Because of the obstructive phenomenon, retraction was evident in every case and cyanosis in the severer. Examination of the pharynx and larynx revealed no findings, and in most cases the lungs were negative to percussion and auscultation. Two patients demonstrated moist, bubbling rales, and a third, decreased breath sounds. In one patient a roentgenogram of the chest revealed findings consistent with bronchopneumonia. Lethargy and poor feeding were present in several of our patients. The poor feeding was attributed to nasal obstruction. Only one patient manifested fever. No gastrointestinal symptoms were present.

Oxygen and placing of the patient on his abdomen in a Trendelenburg position seemed to be the most efficacious therapy. Nasal decongestants, antihistaminics, and, in some cases, antibiotics were also used, but their role was not impressive.

For the most part the toxic reaction appeared to be self-limited, lasting from one to five days. However, there were two deaths in this group. One of these will be described below. In the other patient who died, although we do not believe that any medication was the direct cause of death, it did appear to have a contributory role. In this

case subarachnoid bleeding, presence in the alveoli of desquamated epithelial cells, and generalized vascular dilatation were demonstrated on postmortem examination.

Two cases are reported below. The first is an example of the mild state which 10 of our patients exhibited. The second is of the severe type.

CASE 11 (Table).—A full-term Negro boy; birth weight 8 lb. 2 oz. Spontaneous, vertex delivery. The mother of this patient received meperidine and vinbarbital intramuscularly and reserpine intravenously one hour prior to delivery. Nasal discharge with thoracic retraction and stertorous breathing were noted 21 hours after delivery. Physical examination showed no other abnormalities. The infant was treated with positioning only. Symptoms subsided within 24 hours.

CASE 9 (Table).—A full-term Negro boy; birth weight 6 lb. 5 oz. Spontaneous vertex delivery. The mother of this patient received 10 mg. of reserpine intravenously 16 hours before delivery and no other drugs. Nasal congestion, noisy breathing, and subcostal retraction were noted 12 hours after birth. This infant's skin appeared slightly cyanotic. and his acivity was decreased. Choanal atresia was ruled out by the uninhibited passage of catheters from the anterior nares into the nasopharynx. Examination of the lungs revealed adequate air exchange, with transmitted rhonchi from the upper respiratory passages. Laryngoscopy revealed no abnormalities. Treatment consisted of water nebulization, oxygen, broad-spectrum antibiotics, and nose drops. The following day he was worse and fed poorly, necessitating gavage feedings. The patient was placed in the Trendelenburg position on his abdomen. His condition gradually declined, and he died at 66 hours of age, with severe cyanosis and increasing respiratory distress.

Postmortem examination revealed desquamated epithelial cells in the alveoli, with areas of atelectasis and emphysema and generalized vascular visceral congestion. Although protein fluid and some hemorrhage were seen in the alveoli, the principal pathologic change did not appear to be an inflammatory process.

COMMENT

"Nasal congestion" is known to be a side-effect of reserpine administration in the adult. As is shown in our Table, the mother of each infant presented received reserpine intravenously prior to delivery. Other drugs were given, but, reserpine was the only one common to all of them, and in fact two mothers received no drugs other than reserpine.

We feel that reserpine has a definite effect in the newborn infant of mothers who received it prior to delivery. There was a total of 77 mothers who received reserpine alone or in combination with other drugs during this period. Sixteen per cent of the infants of these mothers had toxic symptoms, while the mothers themselves showed no reactions. Furthermore, several infants, including twins, since that time have demonstrated nasal discharge, and on investigation it was found that reserpine had been administered to the mothers prior to delivery.

It appears therefore that this is either a sensitivity peculiar to the newborn or that it is due to rapid accumulation of the drug in the infant via the placenta. All these mothers received the drug within two days of delivery. There does not appear to be any correlation between amount administered, time of onset, and severity of symptoms.

Microscopic examination of the lungs of the two patients who died showed alveoli containing desquamated epithelial cells, erythrocytes, and some protein material. This did not appear to be principally inflammatory, nor were there findings of hyaline-membrane disease or simple aspiration.

There also appears to be a generalized vascular dilatation of the capillaries and venules which may be a secondary effect of anoxia, a result of the drug alone,[2] or a result of both of these factors.

SUMMARY AND CONCLUSIONS

A group of 13 newborn infants is described. In 12 of these infants reserpine had been administered to the mothers prior to delivery. Their clinical symptoms are described, and it is concluded that reserpine may have an untoward effect in the newborn, manifested by nasal discharge, retraction, lethargy, and anorexia.

REFERENCES

1. Wilkins, R. W.; Judson, W. E.; Stone, R. W.; Hollander, W.; Huckabee, W. E., and Friedman, I. H.: Reserpine in the Treatment of Hypertension: A Note on the Dosage and Effects, New England J. Med. **250**:477-478 (March 18) 1954.

2. Chopra, R. N; Gupta, J. C., and Mukherjee, B.: The Pharmacological Action of an Alkaloid Obtained from Rauwolfia Serpentina, Benth: Preliminary Note, Indian J. M. Res. **21**:261-271 (Oct.) 1933.

3. Freis, E. D., and Ari, R.: Clinical and Experimental Effects of Reserpine in Patients with Essential Hypertension, Ann. New York Acad. Sc. **59**:45-53 (April 30) 1954.

4. Reference deleted.

5. Freis, E. D.: Mental Depression in Hypertensive Patients Treated for Long Periods with Large Doses of Reserpine, New England J. Med. **251**:1006-1008 (Dec. 16) 1954.

6. Hafkenschiel, J. F., and Sellers, A. M.: Intravenous Reserpine in Patients with Essential Hypertension, Ann. New York Acad. Sc. **59**:54-60, (April 30) 1954.

7. Moyer, J. H.: Cardiovascular and Renal Hemodynamic Response to Reserpine (Serpasil), and Clinical Results of Using this Agent for the Treatment of Hypertension, Ann. New York Acad. Sc. **59**:82-94 (April 30) 1954.

Portal Hypertension in Infants and Children

DAVID YI-YUNG HSIA, M.D.
and
SYDNEY S. GELLIS, M.D., Boston

Portal hypertension may be defined as a condition which develops in response to obstruction to portal blood flow. This may be caused by thrombosis or abnormalities in the portal vein or its tributaries or by obstruction within the liver itself. The primary clinical manifestations are splenomegaly and hemorrhage from varices. Both develop in direct response to the increased portal pressure. Ascites, although commonly seen in patients with cirrhosis, does not bear as direct a relationship to elevated portal pressure as was formerly believed, developing as a manifestation of hepatic decompensation frequently seen in association with portal hypertension.[1]

Although Stahl,[2] as early as 1748, had observed that the portal vein, the spleen, and hemorrhoids were related in a vaguely described disease syndrome, it was not until the beginning of the present century that the concept of portal hypertension was actually suggested. Preble [3] presented a well-documented report of 60 patients with cirrhosis of the liver who succumbed to massive gastrointestinal hemorrhage. Varices were demonstrated at autopsy in 80% of these patients, and Preble postulated that these appeared in response to increasing pressure within the portal system. Although similar observations were made by Heller,[4] Warthin,[5] de Josselin de Jong,[6] and Enderlein and co-workers,[7] interest in portal hypertension abated, and little reference to the subject can be found until a number of years later.

In 1936, Rousselot [8] reported success in measuring the pressure in the splenic veins of patients with splenomegaly, finding it elevated many times above normal limits. These observations were confirmed by Thompson and his co-workers,* and also showed that portal hypertension results from a variety of primary lesions and that cirrhosis of the liver is only one of several obstructive mechanisms. In 1945, Whipple [11] proposed that all patients with portal hypertension be placed in two clinical groups: those in whom the obstruction is due to intrahepatic disease and those in whom the obstruction lies outside the liver. By far the greater number of patients fall into the first category, with the obstruction caused by cirrhosis. In this condition, compression of the intrahepatic vessels by fibrous tissue raises the resistance to the flow of blood through the liver. As a result of the rise in the pressure in the portal system, blood is forced into channels connecting the portal vein and systemic veins, with the production of varices.[12] Extrahepatic block may occur as a result of malformation or of thrombosis of the portal, superior, mesenteric, or splenic veins.

Portal hypertension due to extrahepatic block has been extensively studied in infants and children. In 1927, Smith and Howard [13] reported five children with splenomegaly in whom the first symptom of disease was severe gastric hemorrhage. They postulated that the condition may have been caused by sclerosis or phlebitis of the portal veins. Smith and Farber [14] later demonstrated that the primary pathologic lesion was portal or splenic vein

Submitted for publication Aug. 4, 1955.

Aided by a grant from the Playtex Park Research Institute.

From the Department of Pediatrics, Harvard Medical School, and the Children's Medical Center.

* References 9 and 10.

obstruction caused in most instances by thrombophlebitis secondary to infection arising in some other part of the body. Similar cases were reported in children by Wallgren,[15] van Creveld and Levy,[16] and Nobel and Wagner [17] in Europe at about the same time. It should be pointed out that although Banti † was probably referring to this condition when he wrote his classic paper defining the syndrome which bears his name, the term "Banti's disease" connotes such a multiplicity of lesions to different physicians that it is best to avoid confusion by completely abandoning the appellation.

Although omentopexy and splenectomy are of some value in relieving portal hypertension and preventing the bleeding from esophageal varices, the benefits are usually transient, and bleeding recurs frequently. The modern era in the treatment of portal hypertension began when Whipple [11] and Blakemore and Lord‡ demonstrated that excessively high levels of pressure within the portal vein could be reduced significantly by either portacaval or splenorenal shunt.

In the past decade, these procedures have been used with considerable success for the purpose of reducing the risk of hematemesis in adults.§ However, in infants and children, the experience has been extremely limited. Shumacker and King [33] have reviewed the courses of 21 patients with primary portal hypertension whose symptoms began before the age of 15 years. They showed that four out of five patients who received no treatment died shortly after admission. The fifth patient could not be followed but was having frequent episodes of hematemesis when last seen. Ten patients were treated by splenectomy alone, and hematemesis recurred in all but one of these. Seven patients, including one previously treated by splenectomy alone, were treated by venous shunt procedures, and all except one were doing relatively well. Gross [34] has reported essentially similar experiences.

† References 18 and 19.

‡ References 20 and 21.

§ References 22-33.

DESCRIPTION OF STUDY

The present study included all patients with portal hypertension seen at the Children's Medical Center, Boston, during the 30-year period from 1924-1953. The detailed clinical and pathological findings of patients with portal hypertension secondary to cirrhosis of the liver have been presented in the accompanying paper,[35] and these cases will be discussed only in terms of portal hypertension. The findings in the cases of primary portal hypertension, however, will be described in greater detail.

I. PRIMARY PORTAL HYPERTENSION

Clinical Description.—A total of 21 cases of primary portal hypertension was studied (Table 1). The age of onset varied from 1 to 9 years, and the patients were usually seen between six months and one year after the initial complaint. Hematemesis and tarry stools were presenting symptoms in 16 of the children and marked splenomegaly in 4. In one child the diagnosis of portal hypertension was established only when he was explored surgically after trauma to the abdomen. All of the patients were entirely well and free of symptoms prior to the onset of either bleeding or splenomegaly. None of the patients had ever been jaundiced, and none showed any evidence of previous liver disease.

It is important to note that 9 of the 21 children had a history of purulent infections during the first few weeks of life. These included two cases of omphalitis and peritonitis and one case each of cellulitis of the arm, osteomyelitis, abscess of the foot, suppurative otitis media, and infection following circumcision. In addition, three children had severe respiratory infections and diarrhea during the first weeks of life, bringing to 12 out of 21 the total number of children with severe infection early in life.

All of the children showed splenomegaly which varied from 1 to 12 cm. below the costal margin. In seven of the children there was hepatomegaly, but the enlargement was slight. Only seven of the children developed ascites, and this was usually quite intermit-

tent and not marked. Nineteen of the children had bouts of hematemesis, but in only nine were varices demonstrated by x-ray studies.

Several of the children showed signs of congestive splenomegaly with hypersplenism. In eight, the total white blood cell count was below 4000 per cubic millimeter, and in six, the total platelet count was below 100,000. No significant depression of polymorphonuclear leucocytes was noted. Liver-function tests were normal in 11 of the 13 patients studied; a slight increase in sulfobromophthalein (Bromsulphalein) retention was noted in two patients.

The results of treatment of patients with primary portal hypertension are given in Table 1. Three of the patients were treated with transfusions only. Two died from esophageal bleeding and the third from debilitation, all within a short time after the diagnosis was established. Twelve of the patients were treated by splenectomy alone. Of these, two could not be followed and one died in the immediate postoperative period. Five of the remaining nine patients treated by splenectomy had recurrences of esophageal varices and bleeding. This was sufficiently severe to cause death in two children, six months and one year after splenectomy. In two others, bleeding recurred 9 and 10 years after splenectomy but was successfully managed by transfusions, and both are doing moderately well at the present time. In one other patient, bleeding occurred regularly for the first 10 years after splenectomy, but this gradually improved, and she has had no further bleeding for a period of four years. She has otherwise been entirely well and leads a normal life as a student nurse. Her liver-function tests have been repeatedly negative. Four of the children have had no recurrence of bleeding six months, one, one and one-half, and four years after splenectomy. However, in these one cannot be certain that recurrence will not occur in the future.

Six of the patients have been treated by splenorenal shunt. This was unsuccessful in one patient, and bleeding from varices recurred one year later. Exploration was again done, and the shunt was found to have closed. The other five patients are doing well six months, one, one and one-half, four, and five years after splenorenal shunt and have had no recurrence of esophageal bleeding. Follow-up studies show them to be normal in every way.

Pathological Description.‖—Among the 21 cases of primary portal hypertension 6 of the cases had liver biopsies and in another 6 the liver was examined at postmortem examination. Not one of these livers was cirrhotic, but in four a minimal increase in the fibrous tissue of the portal areas was present. The portal triads were infiltrated by lymphocytes, mononuclear cells, and less often by plasma cells in 7 of the 12 liver specimens, but this was never considered to be more than minimal in any case. In one case with venous valves in the splenic vein granulomata were present in the liver as well as the spleen, but those in the liver were scattered throughout the parenchyma; their true nature is not known. The onset of splenomegaly long antedated (by years) the formation of these inflammatory granulomata.

Of the six cases coming to autopsy all had pathological changes explaining the hypertension within the portal system. In two cases obstructing valves were demonstrated within the lumen of either the splenic vein or the portal veins or both. In three of the autopsied cases there was evidence of thrombosis and fibrous obliteration of the portal vein just proximal to its entrance into the liver. One of these had a double portal vein, one branch of which ran anteriorly to the pancreas and was obliterated by an old organized thrombotic process. The mesenteric veins were acutely thrombosed. In the second case the portal vein was atretic at the point of entrance to the liver, with a few collateral radicals passing along the cystic ducts to enter the liver diffusely. The third case,

‖ The pathologic material was prepared by Dr. John M. Craig, Department of Pathology, Children's Medical Center, Boston.

TABLE 1.—*Primary Portal Hypertension in Children*

Case No.	Past History: Age at Onset, Yr.	Past History: Significant Past History	Presenting Sign or Symptom: Hematemesis	Presenting Sign or Symptom: Splenomegaly	Presenting Sign or Symptom: Others	Physical Signs: Jaundice	Physical Signs: Hepatomegaly	Physical Signs: Splenomegaly	Physical Signs: Ascites	Physical Signs: Varices*	Laboratory Data: Blood Cell Counts: HGB.	Laboratory Data: Blood Cell Counts: WBC	Laboratory Data: Blood Cell Counts: Platelets	Laboratory Data: Liver Function Tests†	Laboratory Data: Other Tests	Course of Disease: Treatment-Age, Yr.	Course of Disease: Length Follow-Up	Course of Disease: Ultimate Course
1	7	None	+	..	.....	0	½	2	0	+	5.6	8.7	190,000	.....	Fragility normal	Splenectomy-7	.....	Died of pneumonia in postop. period
2	5	None	+	..	Purpura	0	2	10	0	++	10.8	3.7	64,000	.....	Fragility normal	Splenectomy-5	.....	Unknown
3	8	None	+	..	.....	0	0	3½	0	++	10.9	3.0	112,000	.....	.....	Splenectomy-8	.....	Unknown
4	9	Suppurative otitis media in infancy	+	+	Anemia	0	0	4	0	+	11.5	2.1	85,000	Normal	BSP. normal; TP. 7.5 gm./100 cc.	Splenectomy-10	10 yr.	Recurrence of varices at 20 yr.
5	5	None	+	+	.....	0	0	12	0	++	....	....	.....	Normal	.....	Splenectomy-5	14 yr.	Recurrence of varices for 10 yr.; gradually subsiding
6	5	Infection after circumcision at 1 wk.	..	+	Abdominal pain	0	0	3	0	+	13.1	14.8	781,000	Normal	.....	Splenectomy-5	9 yr.	Recurrence of varices at 14 yr.
7	1	Peritoneal abscess at 5 mo.	..	+	.....	0	0	8	0	++	14.4	6.9	48,000	.....	A/G 4.6/2.4	Splenectomy-5½	4 yr.	Doing well at 9½ yr.
8	9	None	+	+	.....	0	0	6	0	++	6.0	12.2	Adq.	Normal	A/G 5.0/1.6; BSP. 20%	Splenorenal shunt-9	4 yr.	Doing well at 13 yr.
9	6	Purulent umbilical infection at 1 mo.	+	..	Pallor	0	2	3½	0	+	13.5	3.6	136,000	Normal	BSP. normal; prothrombin normal	Splenorenal shunt-6	3 yr.	Doing well at 11 yr.
10	5½ mo.	Cellulitis of arm at 2 mo.	+	..	Tarry stools; abd. enlargement	0	4	5	+	++	9.0	8.6	Adq.	Normal	BSP. normal; TP. 6.6 gm./100 cc.	Splenorenal shunt-4	1½ yr.	Recurrence of varices following closure of shunt at 5 yr.
11	10 mo.	Osteomyelitis at 4 wk.	+	+	.....	0	0	6	+	++	12.6	6.0	71,000	SL. positive	.....	Splenectomy-3	1 yr.	Doing well at 4 yr.
12	2	Peritonitis at 3 wk.	+	..	Tarry stools	0	1	1	0	++	....	....	Adq.	Normal	.....	Splenectomy-2	6 mo.	No change at 2½ yr.
13	5½	Omphalitis at 3 wk.	+	..	Tarry stools	0	1	2½	0	+	9.0	....	Adq.	Normal	.....	Splenorenal shunt-5½	6 mo.	Doing well at 6 yr.
14	1½	Pertussis at 1½ yr.	+	..	Ascites	0	½	3	+	+	8.4	8.5	165,000	.....	.....	Splenectomy-1½	1 yr.	Died at 2½ yr. of acute bleeding
15	4	Abscess on foot at 3 wk.	+	+	.....	0	1	8	+	+	4.2	29.9	Adq.	.....	A/G 4.0/4.6	Splenectomy-7	6 mo.	Died at 7½ yr. of acute bleeding
16	4	None	..	..	Abdominal pain; tarry stool	0	0	8	+	+	8.1	3.2	50,000	.....	.....	Supportive	6 mo.	Died at 5 yr. of acute bleeding
17	1	Diarrhea at 1 wk.	+	+	.....	0	0	1½	0	+	10.0	8.3	Adq.	.....	.....	Supportive	.....	Died at 1 yr. of hemorrhage
18	4	Diarrhea and fever in infancy	+	+	.....	0	1	3	0	++	11.8	5.5	Adq.	Normal	A/G 3.8/3.1; BSP. 20%	Splenorenal shunt-11	2 yr.	Doing well at 13 yr.
19	9	None	..	+	Abdominal pain	0	2	12	+	0	9.5	2.8	Adq.	Normal	A/G 3.1/1.7; BSP. Normal	Supportive	1 mo.	Died at 14 yr. of liver failure
20	6	None	..	..	? trauma to spleen	0	1½	6	0	0	9.0	2.8	41,000	SL. positive	.....	Splenectomy-6	1½ yr.	Doing well at 7½ yr.
21	2	Resp. infection at 1 yr.	..	+	Pallor	0	3	6	+	++	7.9	2.9	63,000	Normal	A/G 4.9/3.1	Splenorenal shunt-2½	1½ yr.	Doing well at 4 yr.

* ++ indicates confirmed by barium swallow.
† Liver function tests include thymol turbidity, thymol flocculation, cephalin-cholesterol flocculation, and one-minute and total serum bilirubin.

with thrombotic obstruction of the portal vein, had recanalized the main portal vessel with the formation of small subsidiary channels in the portal vein. In this case thrombosis of the superior sagittal cranial sinus had also occurred, with resulting encephalomalacia. In the last case the portal vein did not enter the liver but passed through it to join the hepatic vein. The mechanism of hypertension was not obvious in this case, since no thrombosis or obstruction was found, although the child died with massive bleeding from esophageal varices and with a typical congestive splenomegaly.

In the entire group of 21 cases in which the spleens were available for study, they were two to seven times heavier than the normal weight for age and had an unusual firmness to palpation with often a grossly observable fibrosis to the capsule. Microscopically, increases in capsular, subcapsular, and peritrabecular fibrous tissue were noted; these were extreme in about one-half the cases. The reticulum pattern of the red pulp was nearly always greatly thickened; in only a single case was the latter change judged to be minimal. The congestion was generalized in the red pulp in only a single case, the formation of "lakes" of distended sinusoids in the peripenicillar areas was present in 10 instances. These became thrombosed and organized in five cases, with formation of iron-encrusted collagenous spicules (Gamma Gandy bodies) in two cases. The sinusoidal reticuloendothelial cells were swollen and proliferated in 18 cases, yet active erythrophagocytosis was found in but 5 cases.

SECONDARY PORTAL HYPERTENSION

Clinical Description.—In the accompanying paper,[35] which reviews cirrhosis of the liver in infants and children, secondary portal hypertension was noted in one-fourth of the cases reported. The incidence of this complication and the signs and symptoms in each of the groups of cirrhosis are summarized in Table 2.

All of the patients showed the characteristic signs and symptoms of portal hypertension. This included splenomegaly in 21 cases (96%), esophageal varices in 14 cases (64%), and signs of congestive splenomegaly with decrease of the blood elements in 5 cases (23%). In addition, ascites occurred in 12 cases (54%). As a rule, the signs and symptoms of portal hypertension appeared late in the course of the disease, frequently terminally.

TABLE 2.—*Secondary Portal Hypertension in Infants and Children*

	Incidence			Signs and Symptoms			
	Total Cases	Cases with Portal Hypertension	Per Cent	Varices	Splenomegaly	Ascites	Blood Changes
A. Cirrhosis associated with hepatitis							
1. Cirrhosis following neonatal hepatitis	9	3	33	3	3	3	0
2. Cirrhosis following viral hepatitis	8	6	75	4	6	2	1
3. Cirrhosis without predisposing illness	13	8	62	2	7	4	4
B. Obstructive cirrhosis	61	5	8	5	5	3	0
C. Cirrhosis due to miscellaneous causes	7	0	0	0	0	0	0
Total	98	22	22	14	21	12	5

As in primary portal hypertension, the patients with secondary portal hypertension were treated in three different ways (Table 3): (1) Seventeen of the 22 patients (80%) were treated by supportive measures, such as diet, vitamins, transfusions, paracentesis, and omentopexy. No other definitive treatment was instituted in these patients because approximately half of the infants were of an age group in which the splenic vein was considered too small for successful anastomosis and because some of the patients were seen prior to the era when venous shunting became an established procedure. Of these 17 patients, 16 have died either as a result of

further bleeding from varices or from progressive liver failure. One is still alive, but has increasing jaundice, ascites, and frequent hematemesis. (2) One patient with cirrhosis following viral hepatitis was treated by splenectomy alone. This was done because of increasing splenomegaly and a low white blood cell count and platelet count. She has done moderately well since splenectomy, although she remains slightly anemic and bleeds excessively during menstrual periods. (3) Four of the patients were treated by splenorenal shunt. All four have done well postoperatively. One patient with cirrhosis

TABLE 3.—*Results of Treatment of Portal Hypertension in Infants and Children*

	Supportive				Splenectomy				Splenorenal Shunt					Total				
	No. Cases	Died	Unimproved	Living and Well	No. Cases	Died	Unimproved	Living and Well	No. Cases	No Follow-Up	Died	Unimproved	Living and Well	No. Cases	Died	Unimproved	Living and Well	No Follow-Up
Primary portal hypertension	3	3	0	0	12	1	5	4	2	6	0	1	5	21	4	6	9	2
Secondary portal hypertension																		
1. Cirrhosis following neonatal hepatitis	2	2	1	0	0	0	0	0	0	0	0	0	0	2	2	1	0	0
2. Cirrhosis following viral hepatitis	4	4	0	0	1	0	0	1	0	1	0	0	1	6	4	0	2	0
3. Cirrhosis without predisposing illness	5	5	0	0	0	0	0	0	0	2	0	0	3	8	5	0	3	0
4. Obstructive cirrhosis	5	5	0	0	0	0	0	0	0	0	0	0	0	5	5	0	0	0
Total secondary portal hypertension	17	16	1	0	1	0	0	1	0	4	0	0	4	22	16	1	5	0
Total all cases	20	19	1	0	13	1	5	5	2	10	0	1	9	43	20	7	14	2
Per cent of group	..	95	5	0	..	7	39	39	15	..	0	10	90	..	46	17	32	5

of the liver following viral hepatitis proved by biopsy has been followed for four years and has not only been well in every way, but liver function tests have reverted from a strongly positive pattern to a normal one following operation. Three others with cirrhosis of the liver of undetermined origin have been followed for five and one-half, two and one-half, and two years after splenorenal shunt. All are doing well, although their liver function tests continue to be positive. One of these children developed homologous serum hepatitis following a transfusion, but made an uneventful recovery.

Pathological Description.—This has been extensively covered in the accompanying paper.[35]

COMMENT

Portal hypertension is manifested by two principal signs: (1) enlargement of the spleen, which may cause depression of one or more of the circulating blood elements, and (2) dilatation of the collateral venous channels (varices), which when ruptured will cause massive hemorrhage manifested by hematemesis and the passage of tarry black stools.

Once the diagnosis of portal hypertension is made, it is essential to differentiate between that which is primary and that which is secondary to cirrhosis of the liver. As a general rule, the following points suggest primary portal hypertension:

1. History of omphalitis or severe bacterial infection during early infancy followed by an uneventful course until signs of portal hypertension appear.
2. An essentially negative and benign history prior to the onset of signs of portal hypertension.
3. Hematemesis and/or splenomegaly as the presenting complaint.
4. No evidence of jaundice or other signs of liver disease prior to onset of symptoms.
5. Normal liver function tests.

In contrast, the following suggest that the portal hypertension is secondary to cirrhosis of the liver:

1. A previous history of jaundice or liver enlargement.

2. Hepatomegaly and tenderness of the liver, which is prominent, and usually appears prior to the onset of splenomegaly.
3. Ascites and other evidences of liver failure, tending to appear prior to signs of portal hypertension.
4. Positive liver function tests.

Hematemesis is usually not a presenting symptom in portal hypertension secondary to cirrhosis, although splenomegaly may be noted when the patient is first seen.

From a practical point of view only portal hypertension secondary to cirrhosis without apparent predisposing illness poses a problem for differential diagnosis from primary portal hypertension, since jaundice is usually a prominent feature of all of the other types of cirrhosis with portal hypertension. Liver-function tests are extremely useful in differentiating these two, since in primary portal hypertension they tend to be negative, whereas in cirrhosis without predisposing illness they tend to be positive. However, in the occasional patient, it may be impossible to differentiate the two clinically, and the type of portal hypertension can only be determined by liver biopsy.

The differential diagnosis between primary and secondary portal hypertension is important mainly from the viewpoint of treatment. There is considerable evidence that primary portal hypertension should be treated by a venous shunt. Although the present series is too small to be definitive, the experience presented by others in adults ¶ and children [33] shows the beneficial effect of such therapy. The improvement in the five out of six patients treated in this way in the present series supports this approach.

Three factors must always be considered in connection with the surgical treatment of primary portal hypertension. First, splenorenal shunt is the operation of choice in the pediatric age group. The procedure can be done with relative ease and does not interfere with normal growth and development. Second, the operation will only be successful if the splenic vein is of a sufficient size anatomically to permit an anastomosis to be made regardless of age. As a rule the operation is less likely to be successful in infants and children under the age of 3 years. If the size of the vessel is in doubt, portagrams [29] should be taken at the operating table, and if the vessels are of insufficient size, the operation should be postponed until the child is larger or another type of venous shunt, such as portacaval, should be considered.[37] Finally, and most important of all, if a splenectomy is to be done because of hypersplenism, a splenorenal shunt should be seriously considered if any important degree of portal hypertension is found at operation (either by visible engorgement of veins or by actual pressure readings with a manometer). Once splenectomy has been performed, the splenic vein can never at some future date be used for anastomosis should that become necessary. It is clear that a much larger number of patients would be required to determine the advantage of a shunt procedure over simple splenectomy in the present series, but the data presented by Shumacker and King [33] are markedly in favor of a venous shunt.

The exact role of shunt procedures in the treatment of portal hypertension secondary to cirrhosis of the liver in infants and children requires further evaluation. In adults, Rousselot [32] and others # have suggested that surgical therapy can be undertaken if there is (*a*) minimal or no ascites, (*b*) minimal degree of absence of icterus, and (*c*) reasonable evidence of hepatic reserve as indicated by appropriate liver-function tests. In patients with advanced cirrhosis of the liver, the mortality rate has been extremely high, both in the immediate postoperative period and during the first few months after the procedure.

Cirrhosis of the liver in infants and children appears to differ considerably from that seen in adults.[15] Alcoholism and nutritional deficiencies do not play a major role in the

¶ References 13 and 14.

References 13 and 14.

etiology of the disease, at least in this country, but hepatitis, probably of the viral type, accounts for many of the cases of secondary portal hypertension. In the present series, four were treated by splenorenal shunt and one by splenectomy alone. All have done well since surgery. However, it should be pointed out that all were in fairly good condition prior to surgery and fitted into the group considered suitable for shunt procedures. In contrast, the patients who did not undergo surgery had a catastrophic course. Sixteen of the seventeen who received supportive therapy alone have died as a result of the disease, and the remaining patient is terminally ill with cirrhosis. Whether or not some of these patients might have benefitted by surgical intervention remains unknown.

The authors believe that, since there is little effective medical therapy in the treatment of children with portal hypertension secondary to cirrhosis of the liver at the present time, an attempt should be made whenever possible to establish a venous shunt, with the full realization that this procedure may carry a high operative mortality owing to severe liver damage and with no striking proof that many, if any, of the cases will benefit from the procedure. Since the alternative of no therapy carries a hopeless prognosis, the establishment of a venous shunt appears to justify the risk involved.

During recent months, Habif and coworkers [30] and Davidson [80] have shown that with ion-exchange resins and a low-sodium diet as preoperative preparation, more patients can be brought into sufficiently good condition to permit surgery, even though previously they would have been considered poor risks. This may be helpful in lowering the mortality associated with shunt procedures.

SUMMARY

A total of 43 cases of portal hypertension in infants and children seen at the Children's Medical Center over a 30-year period has been investigated.

Twenty-one of these were found to have primary portal hypertension due to extrahepatic obstructions. A history of omphalitis and sepsis during early infancy, early hematemesis and splenomegaly, the absence of clinical jaundice, and frequent depression of the blood elements were prominent features of this type of portal hypertension. Of the six coming to autopsy, all had anatomical lesions which could account for the condition.

Twenty-two others were found to have portal hypertension secondary to cirrhosis of the liver. Hepatitis appeared to be the commonest etiological agent, and in many of these cases liver function tests were usually strongly positive.

Venous shunt appears to be the treatment of choice in children with primary portal hypertension. Since the prognosis of those with secondary portal hypertension appears to be uniformly poor with supportive therapy alone, it is felt that venous shunt should also be employed in this group of patients.

Dr. Sidney Farber provided the pathological material for this study.

REFERENCES

1. Child, C. G., III: The Hepatic Circulation and Portal Hypertension, Philadelphia, W. B. Saunders Company, 1954, pp. 210-211.

2. Stahl, G. E.: The Portal Veins, in von Haller, A.: Disputationes anatomicae selectae, Göttingen, 1748, Vol. 3, p. 131.

3. Preble, R. B.: Conclusions Based on 60 Cases of Fatal Gastro-Intestinal Hemorrhage Due to Cirrhosis of the Liver, Am. J. M. Sc. **119**:263, 1900.

4. Heller, A.: Traumatic Thrombosis of the Portal Vein, Verhandl deutsche. path. Gesellsch. **7**:182, 1904.

5. Warthin, A. S.: Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anæmia and Banti's Disease, Internat. Clin. **4**:189, 1910.

6. de Josselin de Jong, R.: On the Consequences of Thrombosis in the Region of the Portal System, Mitt. Grenzgeb. Med. u. Chir. **24**:160, 1911.

7. Enderlen, Hotz, and Magnus-Alseben: The Pathology and Therapy of Portal Obstruction: Investigation on the Eck Fistula, Ztschr. ges exper. Med. **3**:223, 1914.

8. Rousselot, L. M.: The Rôle of Congestion (Portal Hypertension) in So-Called Banti's Syndrome: A Clinical and Pathologic Study of 31

Cases with the Late Results Following Splenectomy, J. A. M. A. **107**:1788, 1936.

9. Thompson, W. P.; Caughey, J. L.; Whipple, A. O., and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), J. Clin. Invest. **16**:571, 1937.

10. Thompson, W. P.: The Pathogenesis of Banti's Disease, Ann. Int. Med. **14**:255, 1940.

11. Whipple, A. O.: The Problem of Portal Hypertension in Relation to Hepatosplenopathies (E. Starr Judd Lecture), Ann. Surg. **122**:449, 1945.

12. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice: A University of Toronto Text in Applied Physiology, Baltimore, The Williams & Wilkins Company, 1943, p. 480.

13. Smith, R. M., and Howard, P. J.: The Early Occurrence of Gastric Hemorrhage in Children with Splenomegaly, Am. J. Dis. Child. **34**:585, 1927.

14. Smith, R. M., and Farber, S.: Splenomegaly in Children with Early Hematemesis, J. Pediat. **7**:585, 1935.

15. Wallgren, A.: Contribution to the Study of Splenomegaly in Infancy, Acta pædiat. (Suppl.) **6**:1, 1927.

16. van Creveld, S., and Levy, W. A.: Cavernous Malformation About the Portal Vein Manifested Clinically as a Chronic Thrombosis of Splenic Vein, Am. J. Dis. Child. **39**:790, 1930.

17. Nobel, E., and Wagner, R.: Thrombosis and Phlebitis of the Splenic Vein in Childhood (Splenic Vein Stenosis), Ergebn. inn. Med. u. Kinderh. **45**: 1, 1933.

18. Banti, G.: Splenic Anemia, Arch. Scuola d'anat. patol., Firenze **2**:53, 1883.

19. Banti, G.: On Banti's Disease, Folia haemat. **10**:33, 1910.

20. Blakemore, A. H., and Lord, J. W., Jr.: A Nonsuture Method of Blood Vessel Anastomosis: Experimental and Clinical Study, Ann. Surg. **121**: 435, 1945.

21. Blakemore, A. H., and Lord, J. W., Jr.: The Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, Ann. Surg. **122**:476, 1945.

22. Linton, R. R.: The Surgical Treatment of Bleeding Esophageal Varices by Portal Systemic Venous Shunts with a Report of 34 Cases, Ann. Int. Med. **31**:794, 1949.

23. Linton, R. R.: The Selection of Patients for Portacaval Shunts with Summary of Results in 61 Cases, Ann. Surg. **134**:433, 1951.

24. Blakemore, A. H., and Fitzpatrick, H. F.: The Surgical Management of the Post-Splenectomy Bleeder with Extra-Hepatic Portal Hypertension, Ann. Surg. **134**:420, 1951.

25. Blakemore, A. H.: Portacaval Shunt for Portal Hypertension: Follow-Up Results in Cases of Cirrhosis of Liver, J. A. M. A. **145**:1335, 1951.

26. Blakemore, A. H.: Portacaval Shunting for Portal Hypertension, Surg., Gynec. & Obst. **92**: 443, 1952.

27. Moschcowitz, E.: Editorial. Pathogenesis of Hypertension of the Portal Circulation, Am. J. Med. **17**:1, 1954.

28. Welch, C. S.: Medical Progress: Portal Hypertension, New England J. Med. **243**:598, 1950.

29. Rousselot, L. M.; Ruzicka, F. F., and Doehner, G. A.: Portal Venography Via the Portal and Percutaneous Splenic Routes, Surgery **34**:557, 1953.

30. Habif, D. V.; Randall, H. T., and Soroff, H. S.: The Management of Cirrhosis of the Liver and Ascites with Particular Reference to the Portacaval Shunt Operation, Surgery **34**:580, 1953.

31. Ripstein, C. B.: Experiences with Portacaval Anastomosis in the Treatment of Portal Hypertension, Surgery **34**:570, 1953.

32. Rousselot, L. M.: The Present Status of Surgery for Portal Hypertension, Am. J. Med. **16**:874, 1954.

33. Shumacker, H. B., Jr., and King, H.: Splenic Studies: II. Portal Hypertension in Children Associated with Gastroesophageal Hemorrhage, A. M. A. Arch. Surg. **65**:499, 1952.

34. Gross, R. E.: The Surgery of Infancy and Childhood: Its Principles and Techniques, Philadelphia, W. B. Saunders Company, 1953, pp. 559-562.

35. Craig, J. M.; Gellis, S. S., and Hsia, D. Y. Y.: Cirrhosis of the Liver in Infants and Children, A. M. A. Am. J. Dis. Child., this issue., p. 299.

36. Davidson, C. S.: Cirrhosis of the Liver, Am. J. Med. **16**:863, 1954.

37. Hollenberg, H. G., and Briggs, B. P.: Portal Caval Anastomosis in Infants, Ann. Surg. **141**:648, 1955.

Progress in Pediatrics

CIRRHOSIS OF THE LIVER IN INFANTS AND CHILDREN

JOHN M. CRAIG, M.D.
SYDNEY S. GELLIS, M.D.
and
DAVID YI-YUNG HSIA, M.D., Boston

ALTHOUGH many papers have appeared on cirrhosis of the liver, there is only scattered information pertaining to this condition in infants and children. Most of the reports have dealt with a particular type or phase of cirrhosis and have included only a few isolated and often unclassified cases. Nevertheless, as more data accumulate, it appears that cirrhosis of the liver is not as uncommon a disease in infants and children as had originally been believed and that there are certain features in regard to etiology, incidence, and pathogenesis which are more or less characteristic of this age group.*

The identification of the etiologic agent in cirrhosis is frequently difficult if not impossible. Although Laennec's (portal) cirrhosis is common in adults, it occurs rarely in children. A number of specific factors have so far been recognized as being responsible for cirrhosis in infants and children:

1. *Nutritional.*—A chronic deficiency of high-quality proteins and vitamins in the diet may give rise to cirrhosis which appears to take two forms: (*a*) The "infantile biliary cirrhosis" seen in India, which occurs among high-caste Hindu vegetarians, with an onset early in life with ascites, jaundice, an enlarged liver, and an early fatal termination.† It has been suggested that this form may be due to a susceptibility of protein-deficient children to massive necrosis of the liver during hepatitis.[8] Pathologically, these children have a liver with "toxic cirrhosis" or postnecrotic scarring. (*b*) The form that has been described as kwashiorkor in Africa‡ and fatty liver disease in the West Indies.§ This is characterized by an enlarged fatty liver and peripheral nutritional edema. Patients with this disorder develop cirrhosis late in their course, if at all, and often only during young adulthood.

2. *Erythroblastosis.* — Although cirrhosis undoubtedly can occur in isolated instances in this disease,‖ Gerrard [20] has recently shown that it is a relatively uncommon complication of Rh isoimmunization.

3. *Galactosemia.* — In patients with this disease who continue to take lactose, cirrhosis regularly develops.¶ It is interesting to note that a number of the cases originally diagnosed simply as cirrhosis of the liver have in retrospect been found to have galactosemia as the underlying disorder.#

4. *Wilson's Disease.**—Recently, Himsworth [8] and others [30] have suggested that cirrhosis of the liver is not the primary defect in this condition, but may be a reflection of chronic loss of amino acids as has been shown in the de Toni-Fanconi syndrome.[31]

5. *Infections.*[32]—Syphilis, malaria, kala-azar, and chronic intestinal infections have been implicated in tropical countries though not with indisputable evidence as causes of cirrhosis.

Submitted for publication May 19, 1955.

From the Departments of Pathology and Pediatrics, Harvard Medical School, and the Children's Medical Center.

Aided by a grant from the Playtex Park Research Institute.

* References 1-3.

† References 4-7.

‡ References 9-12.

§ References 13 and 14.

‖ References 15-19.

¶ References 21-27.

References 24-26.

* References 31 and 32.

6. *Toxic Damage.*—Chronic poisoning by either heavy metals or organic solvents results in gradual scattered destruction of cells with repair and proliferation of fibrous tissue.[33]

7. *Obstruction.*—Biliary cirrhosis can occur following prolonged obstruction. This may be due to congenital malformations † or external pressure on the extrahepatic ducts. This can also follow inspissation of mucoproteins in cystic fibrosis of the pancreas.‡

8. *Cardiac Cirrhosis.*—This may follow chronic venous congestion and repeated heart failure.§

9. *Hepatitis.*—During recent years, there has been growing conviction that viral hepatitis plays a definite role in the production of portal cirrhosis.‖ Although the relationship has not been well established in children, Sutton,[50] Saffro and Calvin,[51] and Laurie [52] emphasize that cirrhosis of the liver was preceded by an attack of "catarrhal jaundice" in the cases they reported. After World War II, Schindler and Kindschi [53] and Drake [54] showed that cirrhosis of the liver occurred after definite viral hepatitis in a number of the children they studied. Several authors ¶ have reported cases of cirrhosis of the liver occurring after severe jaundice during early infancy, where blood-group incompatibility did not appear to play a definite role. Although they were poorly understood at the time they were reported, many of these cases appear in retrospect to represent the end-result of neonatal hepatitis.#

10. *Glycogen-Storage Disease.*—In certain cases of glycogen-storage disease cirrhosis has been reported,* although in most cases of classical von Gierke's disease cirrhosis is not present.†

11. *Transfusional Siderosis.*—This is an uncommon cause of cirrhosis in children,‡ while true hemochromatosis has to our knowledge not been reported in the pediatric age group.

The purpose of the present paper is to offer a classification of cirrhosis of the liver in infants and children as seen in New England.

This study included all the patients with a diagnosis of cirrhosis seen at the Children's Medical Center during the 30-year period 1924-1953. In all of these liver tissue was available for study, either following a biopsy or post mortem. An equal number of patients with only a clinical diagnosis of cirrhosis were thus excluded from the survey. Each case was studied independently by the clinicians and pathologist. Subsequently, the data were discussed and the diagnosis was established by joint agreement.

TABLE 1.—*Cirrhosis of the Liver in Infants and Children at the Children's Medical Center, Boston, 1924-1953*

1. Cirrhosis associated with hepatitis		30
A. Neonatal hepatitis	9	
B. Viral hepatitis	8	
C. Without previous predisposing illness	13	
2. Obstructive cirrhosis		61
A. Biliary atresia	49	
B. Other obstructions to the extrahepatic bile ducts	5	
C. Fibrosis of pancreas	7	
3. Cirrhosis due to miscellaneous causes		7
A. Glycogen-storage disease	2	
B. Galactosemia	2	
C. Cardiac cirrhosis	1	
D. Cholangitis	1	
E. Hemosiderosis	1	
Total		98

The present paper is limited to a classification of cirrhosis of the liver in infants and children. A companion paper to be published later will discuss the problems of primary and secondary portal hypertension in this age group.[75]

The results of 98 cases surveyed are summarized in Table 1. The cases are divided into three major categories: (1) cirrhosis

† References 34-38.

‡ References 39-41.

§ References 42 and 43.

‖ References 44-49.

¶ References 55-59.

References 32 and 60-64.

* References 65-67.

† References 68-70.

‡ References 71-74.

associated with hepatitis, (2) obstructive biliary cirrhosis, and (3) miscellaneous causes of cirrhosis.

1. CIRRHOSIS ASSOCIATED WITH HEPATITIS

Thirty of the patients were found to have cirrhosis of the liver in association with hepatitis. This group could be subdivided into three separate categories: (*a*) cirrhosis following neonatal hepatitis, (*b*) cirrhosis following viral hepatitis, and (*c*) cirrhosis with postnecrotic scarring where jaundice was not the first presenting symptom.

A. Cirrhosis Following Neonatal Hepatitis

Clinical Description.—Neonatal hepatitis § is a clinical entity characterized by early onset of jaundice during the first weeks of life, acholic stools, dark urine, and moderate hepatomegaly and splenomegaly. In these infants [77] the urine contains bile, their stools are free of both bile and urobilinogen, and the flocculation tests of liver function are usually negative. The one-minute and total serum bilirubin, however, are always elevated, and show either a slowly falling or a variable trend. In studying the pathology of this disease, Craig and Landing [61] have shown the presence of inflammatory degenerative changes accompanied by multinucleated giant parenchymal cells diffusely distributed throughout the lobules of the liver and have interpreted these changes as being consistent with those of viral hepatitis. The etiologic agent causing this form of hepatitis has been transmitted to human volunteers [60] from both the mother and her infant and appears to be a strain of the virus of homologous serum hepatitis. The intriguing hypothesis [64] that neonatal hepatitis is caused by the transplacental passage of this virus from the mothers who are silent carriers requires further confirmation.

Nine of the infants developed cirrhosis of the liver immediately following a typical episode of neonatal hepatitis ‖ (Table 2). The

TABLE 2.—*Clinical Course of Cirrhosis Following Neonatal Hepatitis*

Case No.	Signs and Symptoms					Laboratory Tests				Treatment		Ultimate Course	
	Age at Onset	Acholic Stools	Dark Urine	Size of Liver *	Size of Spleen *	Flo. Tests †	Serum Bilirubin ‡	Liver Biopsy	Surg. Expl.	Cholagogues	Age at Death	Cause
1 §	Birth	+	+	3	1	—	—	—	—	—	1 mo.	Diarrhea; liver failure
2	Birth	+ +	+ +	6	3	—	—	—	—	—	4 mo.	Liver failure
3	4 wk.	+ +	+ +	5	0	—	—	—	+	—	3 mo.	Cholangitis; postop.
4	Birth	+	+	2	1½	—	—	—	+	—	4 yr.	Cerebral edema; cirrhosis at autopsy
5	2 mo.	+ +	+ +	6½	1	Neg.	6.9/12.5	+	+	+	2 yr.	Ascites; varices
6 ‖	1 wk.	+ +	+ +	3	0	Neg.	4.3/7.3	+	+	+	3 yr.	Ascites; varices
7	2 wk.	+ +	+ +	7½	0	Neg.	5.8/11.1	+	+	+	6 mo.	Liver failure
8	5 wk.	+ +	+ +	4	0	Neg.	5.6/6.6	+	+	+	3½ yr.	Ascites; varices
9 §	Birth	+ +	+ +	3½	1½	—	—	—	—	—	1 mo.	Liver failure

* In centimeters below costal margin.
† Cephalin, thymol flocculation tests, thymol turbidity.
‡ Expressed in mg. per 100 cc. Hour-minute/total.
§ Patient also had erythroblastosis fetalis.
‖ Sibling also had neonatal hepatitis with cirrhosis.

§ References 38, 61, 64, and 76.

‖ One of these cases was seen through the courtesy of Dr. G. R. Hennigar, of the Medical College of Virginia.

cirrhosis developed in three different ways: (1) In five infants, the process occurred rapidly following the initial illness. In these, although cirrhosis was moderately advanced in the infants at postmortem examination when they died at 1 to 6 months of age, there was insufficient time for the usual clinical signs, such as splenomegaly, ascites, and varices, to develop. (2) In three others, cirrhosis developed more gradually. Two of these eventually died from bleeding esophageal varices at 2½ and 4¼ years, and the third child is still alive at 2½ years of age, but shows evidence of ascites and marked cirrhosis. (3) In the remaining patient, the process appeared to have halted. A diffuse cirrhosis was unexpectedly found at autopsy. The child died of an unrelated condition.

Two of the infants had erythroblastosis in addition to neonatal hepatitis. These have been reported upon previously in a series outlining the progression of the changes in the liver to cirrhosis in a group of fatal cases of erythroblastosis.[19] Upon reexamination, their erythroblastotic state is confirmed, but these patients have in addition to cirrhosis active changes of hepatitis, by both their clinical course and the pathologic findings. This is in agreement with Gerrard's recent survey,[20] which showed that cirrhosis is a relatively uncommon sequela of Rh isoimmunization, and, in our experience, with the syndrome of prolonged jaundice following erythroblastosis [28] all of the patients made uneventful recoveries.

Pathology.—In contrast to the succeeding group, the livers of these patients were above the normal weight (1.1 to 1.5 times the normal) for the age, perhaps because of the more precipitous terminal course. Two had grossly nodular surfaces, two had finely granular surfaces, whereas the remaining cases had smooth external appearances. All had an increased resistance to cutting and displayed an increased prominence of the lobular pattern on the cut surfaces.

The tendency microscopically to maintain a semblance of the original lobular patterns without regenerative nodules was strong in this group, except in two of the older children. Distortion of liver-cell cords was, however, a prominent feature of the cases. Periportal scarring was marked in three infants, again in those with a longer duration of life; in the remainder, the periportal fibrosis was almost the minimum compatible with diagnosis. In the less far advanced yet more actively inflammatory cases, a spread of the fibrosis into the parenchymal areas was a prominent feature, and a diffuse thickening of the reticulum throughout the parenchymal lobule with isolation of individual cells was often noted. The active progression of the disease at the time of death was apparent in the frequency of inflammatory and degenerative changes among the hepatic cells; indeed, only two showed no such activity. Bile-duct proliferation of significant degree was found only once, though bile stasis was present in five instances. In two cases no postmortem examinations were done, but in the specimen of the liver removed at biopsy the typical changes of neonatal hepatitis were present; these patients subsequently developed typical clinical signs and symptoms of cirrhosis. In two others early biopsies as well as autopsies were obtained, and a progression of the lesion from the typical neonatal hepatitis could be observed in the sections.

A typical case history follows.

K. P., a white girl, was first admitted to the Children's Medical Center at 4 weeks of age because of increasing jaundice.

Past history revealed that she was the first child of a healthy 28-year-old woman who had an uneventful pregnancy. Delivery was normal, and the infant weighed 7 lb. 7 oz. at birth. The family history was significant in that neither the mother nor any other members of the family had ever been jaundiced or anemic. The present illness began on the third day of life, when the infant was noted to be jaundiced for the first time. The jaundice persisted and became severer prior to admission. The stools were light-colored, and the urine was dark.

Physical examination showed a well-developed and well-nourished, active, icteric infant. The liver was 3 cm. below the costal margin, and the abdomen appeared moderately rounded.

Laboratory studies showed the urine to contain bile, but no urobilinogen. The stools were clay-

colored and free from both bile and urobilinogen. The patient's blood was Group A Rh negative, and the Coombs reaction was negative; the father's, Group B Rh positive, probably heterozygous; and the mother's, Group A Rh positive. Fragility tests showed beginning hemolysis at 0.40 and complete hemolysis at 0.34. The thymol turbidity was 0.5 units, thymol flocculation 0, cephalin-cholesterol flocculation 0, one-minute bilirubin 3.0 mg. per 100 cc., total bilirubin 11.9 mg.

Because of the possibility of biliary atresia, the patient was explored surgically at 6 weeks of age. The extrahepatic biliary system was found to be patent, and both saline and dye were injected successfully into the duodenum from the gall bladder. A liver biopsy was consistent with viral hepatitis. Postoperatively, a small amount of bile was found in the stool. Repeated duodenal intubation, however, showed absence of bile. On discharge from the hospital, the patient was still jaundiced. The icterus appeared to diminish somewhat during the next year, but signs of cirrhosis and esophageal varices developed.

She was admitted for the final time at 2½ years of age because of hematemesis and melena. Despite transfusions and supportive therapy, she developed pneumococcal peritonitis and died.

The sibling of this child also had neonatal jaundice and now has clinical cirrhosis.

At autopsy it was found that this child had an irregularly nodular liver (Fig. 1). A complete remodeling of the lobular pattern was present, with many regenerative lobules (Fig. 2). The portal areas were greatly widened. Many lobules had undergone a terminal hemorrhagic infarction. Portal hypertension was evident in the presence of ascites, dilated abdominal veins, esophageal varices, and a spleen six times the normal weight.

Comment.—Cirrhosis of the liver seems to occur commonly following neonatal hepatitis. In a previous study,[64] we found that 11 of 41 infants (27%) developed cirrhosis as a result of this disease. This high incidence may be due to at least three possible factors: (1) immaturity of the liver in the young infant, (2) infection by homologous serum hepatitis virus, and (3) added insult to the liver from the anesthesia and trauma of surgical exploration, which was undertaken in most of these infants. Since a familial tendency has been observed in cases of neonatal hepatitis,[70] unrecognized cases of neonatal hepatitis may act as precursors of familial cirrhosis.

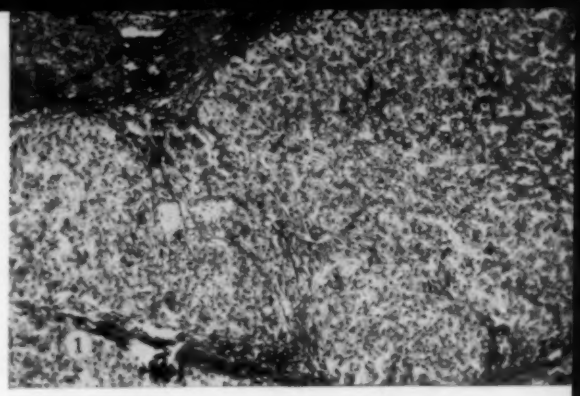


Fig. 1.—Cirrhosis following infantile hepatitis; note areas of hemorrhagic infarction.

B. Cirrhosis Following Viral Hepatitis

Clinical Description.—Eight of the children developed cirrhosis of the liver following an acute attack of viral hepatitis. In each instance, the diagnosis was established by a history of malaise, anorexia, vomiting, fever, abdominal pain, dark urine, light stools, icterus of the skin and sclerae, and an enlarged and tender liver. This was confirmed by positive liver-function tests in five of the cases and by biopsy of the liver in three of them during the acute phase of the disease (Table 3). Two of the patients in the group had received injections or transfusions during the few months preceding the onset of jaundice and may have had homologous serum hepatitis.

In most instances, the initial episode of jaundice was followed by a quiescent period lasting from seven months to four years, during which the patients were free from jaundice and essentially asymptomatic. This was followed by recurrence of jaundice, ascites, and esophageal varices, and eventually the full clinical picture of cirrhosis of the liver. Only one of the children developed congestive splenomegaly with depression of

Fig. 2.—Cirrhosis following infantile hepatitis; reduced ⅓ from mag. × 1110. Hematoxylin and eosin.

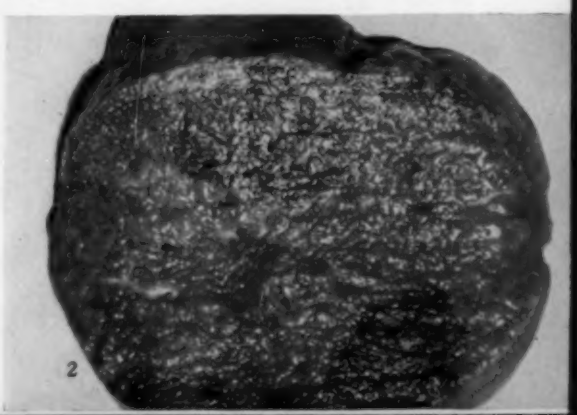


TABLE 3.—*Clinical Course of Cirrhosis Following Viral Hepatitis*

Case No.	Age of Onset	Initial Signs and Symptoms						Liver Function Tests		Blood Cell Count	Liver Biopsy	Treatment	Ultimate Outcome	
		Fever	Anorexia Vomiting	Abd. Pain	Dark Urine	Light Stools	Jaundice	Liver Tenderness	Floc. Tests *	Serum Bilirubin †			Length Followed	Clinical Course
1	5 mo.	+	+	0	+	+	?	?	—	—	N	—	.....	7 mo.	Died from sepsis and interstitial pneumonitis
2	5½ mo.	++	++	0	++	++	++	++	—	Elv./Elv.	N	++	.....	3 mo.	Died from sepsis
3	2 yr.			0					Pos.	—	N		.....	1½ yr.	Died from cirrhosis, ascites, liver failure
4	4 yr.	+	0	0	+	0	+	0	Pos.	7.6/13.0	N	—	.....	2 yr.	Died from bleeding varices
5	9 yr.	?	+	+	+	+	+	?	Pos.	0.14/0.23	WBC 4.0 Plat. 52,000	—	Splenectomy, 1950	4 yr.	Doing moderately well at 13 yr., slight anemia
6	10 yr.	+	+	+	+	+	+	?	Pos.	1.9/2.8	N	—	Paracentesis	16 mo.	Died at 11½ yr. from bleeding varices
7	11 yr.	?	+	+	+	+	+	?	—	—	N	+	.....	14 mo.	Died at 12 yr. from cirrhosis, ascites, liver failure
8	11 yr.	+	+	+	+	+	+	0	Pos.	2.5/4.1	N	—	Splenorenal shunt, 1950	2 yr.	Doing well at 13 yr.; floc. tests reverted to normal

* Cephalin, thymol flocculation tests, thymol turbidity.

† Expressed in mg. per 100 cc.—one-minute/total.

the platelets, but liver-function tests were positive in all five of the children tested.

Six of the eight patients in this group have died. Of these, two died from sepsis, two from bleeding esophageal varices, and two from ascites and liver failure; two are still living and doing moderately well. One of the surviving patients was treated by splenectomy because of congestive splenomegaly. Except for some anemia and excessive bleeding during menstrual periods, she is doing satisfactorily. The other surviving patient was treated by splenorenal shunt because of esophageal varices demonstrated by x-ray studies. She is doing well, and her liver-function tests have reverted to normal postoperatively.

Pathology.—In this group the livers tended to be considerably underweight, being as much as 20%-30% below the normal for the age. In three of four of the autopsied cases there were grossly nodular livers, the nodules ranging from 0.5 to 2.5 cm. in diameter. In only one of the group was cirrhosis not established on histological grounds either at biopsy or postmortem examination; in this case a biopsy showed an active hepatitis, the child later developing classic signs of cirrhosis. Microscopically, all the established cases of cirrhosis contained newly formed regenerative lobules, but in the majority this pattern of regeneration was incomplete and intact original lobules could be recognized in varying numbers. The liver-cell cords were distorted in the regenerative lobules. The liver cells themselves were not unusual in four cases, but in the other three showed the variation in size, shape, and nuclear and necrobiotic patterns associated with active hepatitis. In only a single case, however, was there significant intralobular inflammatory infiltration. The portal fibrous bands were broad in all and conspicuously and irregularly so in all but one case. Again, evidence of progression of the cirrhosis was apparent in the frequency and marked degree of periportal infiltration with chronic inflammatory cells, since only a single case lacked this feature. Bile-duct proliferation was judged

often to be more apparent than real and secondary in large part to collapse of parenchymal lobules, but in two instances it was thought to be moderate to marked in degree.

In all but one of eight cases in which it was available for examination the spleen was enlarged from two to seven times the normal size. Increased thickness of the capsule and trabeculae due to fibrosis was present in all cases, and in two cases fibrotic masses were found occupying organized congestive lakes in the penicillar arteries in which encrustations of iron were present. The lymphoid follicles of the spleen were small in all but two of this group; in these two exceptions the follicles contained a large central mass of immature proliferating cells surrounded by a thin zone of adult lymphocytes, and on the outer border of this rim, a fairly broad zone of immature mononuclear cells. This pattern is said to be found in cases of hypersplenism, which we have also often found to be the case.[78] In a single case terminating in sepsis, there were significant numbers of inflammatory cells present in the pulp.

In this group, two cases had, in addition to postmortem material, biopsy specimens obtained early in the illness. One has already been mentioned above; in the second case a biopsy was done several months before death. This showed more inflammatory activity but a less-advanced degree of cirrhosis (Figs. 3 and 4).

A typical case history follows.

E. M., a 10-year-old girl, was first admitted to the Children's Medical Center with the complaint of fever and jaundice. The history revealed that three weeks prior to admission she developed icterus of the skin and sclerae. This was accompanied by nausea in the mornings, but no other symptoms. Five days prior to admission, she had chills, fever, and abdominal pain, and two days prior to admission she started to vomit.

Physical examination on admission showed the skin and sclerae to be moderately icteric. The liver and spleen were both enlarged, but not tender. Several spider angiomata were noted over the skin.

The blood hemoglobin was 11.4 gm. per 100 cc., the white cell count 8700, with a normal differential; the platelets were normal. The urine urobilinogen was positive in a dilution of 1:64. The stool was positive for bile. The thymol turbidity test

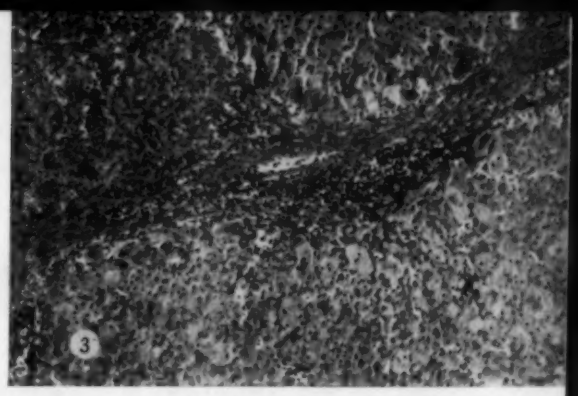


Fig. 3.—Cirrhosis following viral hepatitis. Biopsy specimen taken a few months before death; reduced ⅓ from mag. × 115. Hematoxylin and eosin.

was 20 units, thymol flocculation 3+, cephalin-cholesterol flocculation 4+, one-minute bilirubin 3.5 mg. per 100 cc., total bilirubin 7.1 mg. Febrile heterophile agglutinins were absent. The total protein was 7.2 gm. per 100 cc., and the alkaline phosphatase was 6.0 Bodansky units. Roentgenographic examination of the esophagus by barium swallow showed no varices.

A diagnosis of acute hepatitis was made, and the patient was discharged on bed rest and a high-protein, high-carbohydrate diet with vitamin supplements. She did moderately well during the next 18 months. Her jaundice faded, and her appetite returned. She had no episodes of hematemesis or tarry stools, although one examination of the esophagus by barium swallow showed questionable early varices.

Eighteen months after the previous admission, she awoke at night and vomited approximately a quart of bright red blood. Physical examination on this admission showed a pale, acutely ill patient, who was free from jaundice. The liver was 2 cm. below the costal margin and the spleen 8 cm. below the costal margin. The blood hemoglobin was 10.8 gm. per 100 cc., the white cell count 9600, with a normal differential and 121,000 platelets. The thymol turbidity test was 7.5 units, thymol flocculation 3+, cephalin-cholesterol flocculation 3+, one-minute bilirubin 0.19 mg. per 100 cc., and total bilirubin 0.80 mg.

The patient was treated by transfusions and made a satisfactory recovery. On the 17th hospital

Fig. 4.—Same case as Fig. 3. Autopsy specimen; note progression of the cirrhosis; reduced ⅓ from mag. × 133. Hematoxylin and eosin.

TABLE 4.—*Clinical Course of Cirrhosis Without Previous Disposing Illness*

Case No.	Fam. Hist.	Past History: Age of Onset	Past History: Initial Complaint	Physical Signs: Jaundice	Physical Signs: Hepatomegaly	Physical Signs: Splenomegaly	Physical Signs: Ascites	Physical Signs: Varices	Laboratory: Blood Cell Count	Laboratory: Floc. Tests *	Laboratory: Serum Bilirubin †	Course of Disease: Treatment	Course of Disease: Length Followed	Course of Disease: Ultimate Outcome
1	0	6 yr.	Malaise	0	½	2	0	0	WBC 4.1	—	—	Splenectomy	4 yr.	Died sepsis
2	+	7 yr.	Abdominal pain; hepatomegaly	0	8	3½	0	0	N	—	—	Omentopexy; paracentesis	3 mo.	Ascites, jaundice; died liver failure
3	+	6 yr.	Dyspnea; hepatomegaly	+	6	4	+	+	N	—	—	Paracentesis; omentopexy	2 mo.	Ascites, jaundice; died liver failure
4	0	7 yr.	Epistaxis	0	½	8	+	0	WBC 2.7	—	—	—	4 yr.	Downhill course; died bleeding varices
5	0	1½ yr.	Hepatomegaly	0	3	0	0	0	N	+	0.06/0.13	—	8 yr.	Essential asymptomatic; cirrhosis by biopsy
6	0	6 yr.	Abdominal swelling	0	0	0	+	0	N	+	0.7/2.3	Paracentesis	—	Ascites; died liver failure
7	0	6 yr.	Abdominal pain	0	4½	2	0	0	N	0	0.7/1.4	—	6 mo.	Jaundice; died after exploration
8	0	6 wk.	Epistaxis	0	3	4½	+	0	Platelets 65,000	+	0.7/2.5	Transfusions with alb.	3½ mo.	Bled frequently; ascites; died pneumonia
9	0	8 yr.	Abdominal pain	0	3½	2	0	0	N	+	0.6/1.0	—	6 mo.	No essential change at 10 yr.
10	+	4½ yr.	Epistaxis	0	3	1	0	0	Platelets 42,000	+	0.4/1.2	Splenorenal shunt	5½ yr.	Doing well at 10 yr.
11	+	7½ yr.	Pallor	0	3	8	0	0	Platelets depressed	+	0.4/0.8	Splenorenal shunt	2½ yr.	Doing well at 10 yr. despite homologous serum hepatitis
12	0	11 yr.	Pallor	0	2	8	0	++	N	+	0.8/1.1	Splenorenal shunt	2 yr.	Doing well at 13 yr.; still has pos. floc. tests
13	0	10 yr.	Enlarging abdomen	+	0	10	+	0	N	—	1.8/3.9	Cortisone	4 mo.	Died sepsis

* Cephalin, thymol flocculation tests, thymol turbidity.

† Expressed in mg. per 100 cc.—one-minute/total.

day, a splenectomy and splenorenal shunt were performed and biopsy of the liver was done. Convalescence was uneventful.

She has been followed for two years since the operation and has remained well and free from symptoms. Physical examination shows no icterus, and the liver and spleen are not palpable. The thymol turbidity test is 0, thymol flocculation 0, cephalin-cholesterol flocculation 2+-3+, one-minute bilirubin 0.06 mg. per 100 cc., total bilirubin 0.8 mg.

The specimen of the liver obtained at biopsy was nodular on examination. Microscopically, the liver had large lobules set apart by zones and bands of connective-tissue septa. The regenerative pattern was not complete. Although no inflammation was present within the liver lobules, at the periphery of the lobule a few polymorphonuclear cells, mononuclear cells, and lymphocytes were found. The bile duct proliferation was minimal in amount, and no bile stasis was present.

The spleen was 6.5 times the normal weight; it had microscopically the changes of chronic passive congestion with mild fibrosis, thickening of the reticulum pattern, dilatation of the sinusoids about the penicillar arteries, and encrustation of fibrous tissue by iron deposits.

Comment.—On the basis of clinical findings, it is frequently impossible to decide whether an initial episode of jaundice represents an attack of viral hepatitis or is the first sign of hepatic failure in cirrhosis. One cannot therefore be entirely certain that viral hepatitis is the etiologic agent in this group of cases, although the evidence for it is good. Cirrhosis of the liver appears to be a rare complication of viral hepatitis in children. In a three-year follow-up study of 200 children with known infectious hepatitis we have not encountered a single instance of chronic hepatitis or cirrhosis.‖

C. Cirrhosis Without Previous Predisposing Illness

Clinical Description.—Thirteen of the children in this group were found to have cirrhosis of the liver without any previous episode of hepatitis (Table 4). In two instances, this occurred among siblings. The age of onset varied from 6 months to 11 years, and the disease was gradual and insidious in all the children. In eight, the present complaints were malaise and vague abdominal pain. In four others there was bleeding from either the nose or gums, and in the remaining one, there was a history of diarrhea for six weeks. None of the patients had ever been jaundiced, and none had a history suggestive of hepatitis in the past. A careful survey of past history revealed no other significant contributing factors.

On physical examination, most of the children had enlargement of the liver and spleen. As a rule, hepatomegaly developed first, and as the disease progressed, the liver either remained enlarged or became smaller while the spleen became larger. Ascites developed in four of the patients and esophageal varices in two others.

The flocculation tests were positive in all except one of the children tested. In that patient, they remained with normal limits up to two days prior to death. Serum bilirubin levels were within the normal initially, but became elevated terminally in some of the patients. The albumin-globulin ratio was normal in all five cases tested, while three of five children examined had excessive retention of sulfobromophthalein (Bromsulphalein). One of the patients had a marked prolonged bleeding time, which could not be corrected by the administration of fresh blood, vitamin K, or fibrinogen. Depression of the blood elements was seen in four patients late in the disease when they had marked splenomegaly.

Eight of the patients have died. Of these, six developed ascites and jaundice and died from hepatic failure within six months after the onset of symptoms. The course was more gradual in the other two, one dying from sepsis and the other from bleeding esophageal varices four years after the onset of symptoms. Omentopexy and paracentesis did not materially affect the course of the disease in any of these patients. Three of the patients were treated by splenorenal shunt. They have been followed from two to five and one-half years after the onset of symptoms, and all are doing well clinically. None of them

‖ Hsia, D. Y. Y., and Gellis, S. S.: Unpublished data.

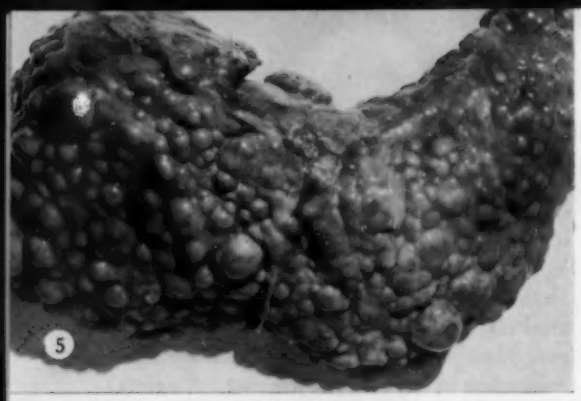
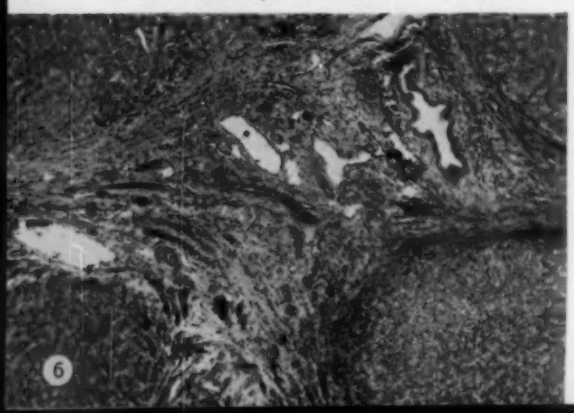


Fig. 5.—Cirrhosis without known previous predisposing illness. Note the large irregular regenerative and persisting lobules of liver parenchyma.

has shown any progression of the disease process, although liver-function tests continue to be positive in all three. It is interesting to note that one of these developed homologous serum hepatitis after receiving a transfusion from a donor who was subsequently proved to be a known carrier of the virus. She made an uneventful recovery. Of the remaining two patients, one has been followed for only six months and cannot, therefore, be properly evaluated. The other patient has shown no essential change clinically for the past eight years. Yet, successive biopsies of the liver done six years apart show marked increase of fibrosis.

Pathology.—In this group autopsy was performed in five cases. In four, there was considerable enlargement of the liver, from 0.25 to 1.0 times over the normal weight. In all, visible nodules measuring 1 to 5 mm. in diameter were present on the external surface, and an irregular accentuation of the lobular pattern was present macroscopically (Fig. 5). Microscopic examination of biopsy and autopsy specimens (Fig. 6) revealed complete distortion of the major lobular pattern in 10 of the 13 cases, while in 3 this was

Fig. 6.—Biopsy. Cirrhosis without known previous predisposing illness; reduced ⅓ from mag. × 110. Hematoxylin and eosin.



partial in character. The regenerative pattern was very irregular in character, with lobules of greatly varying sizes. The widths of the portal triads varied greatly; they were often very broad. The liver-cell cords were also distorted and in keeping with the lobular regeneration. This disturbance in structure was increased by variations in the size of the liver cells as a result of polyploid and necrobiotic changes. Fatty parenchymatous infiltration was not common, but was present in two cases; in one it was marked in many areas; in the other case this fatty change was evident only in the persisting original liver lobules. Evidence of active disease of the liver was not only manifest by variation in the appearance of liver cells, but also by the moderate to marked infiltration peripherally of the entire parenchymal lobular areas with lymphocytes and mononuclear cells and less often by eosinophiles, plasma cells, and polymorphonuclear cells. In two cases such infiltration was judged to be minimal or insignificant. An equivalent inflammatory reaction was present in the portal triads. Bile-duct proliferation, as in the previous group, often seemed more apparent than real and was associated with collapse of the nearby lobules, but still was judged to be significant in 8 of the 13 cases.

It seems obvious that the histological patterns in this group of cases are almost identical to those of the immediately previous group and show, within a fairly wide spectrum, essentially a picture of postnecrotic scarring, with repair and continuing hepatocellular damage. This similarity in appearance is more impressive in view of the considerable disparity in the clinical histories between the groups—on the one hand, a clear-cut history of a preceding attack of jaundice followed by a clear interval and then the development of a clinical cirrhosis in the former group, whereas in the present group the development of cirrhosis was insidious without previously recognized hepatic disease. In two cases biopsy of the liver performed one and five years previous to death showed less cirrhosis but the presence of features suggesting active hepatitis. In eight

cases of this group no significant clinical portal hypertension was present. Of these eight, only four spleens were available for examination. These were all considerably enlarged, ranging in weight from 3 to 10 times the normal, yet surprisingly in only one was there any evidence of an increase in the fibrous tissue or an increase in the reticular elements of the pulp. In three of the four cases, however, there were follicular patterns suggesting the presence of "hypersplenism." Acute congestion of the red pulp was found in two of these four cases. Although generalized congestion of the red pulp was not a feature, the formation of the large lakes of red cells in the regions of the penicillar arteries was present in three cases; in one thrombosis and organization had taken place in some of the lakes.

In the four cases with clinical evidence of portal hypertension, i. e., with ascites and/or varices, in which the spleen was examined pathologically, although there was no greater enlargement (four to seven times), there was an increase in capsular, subcapsular, and trabecular fibrous tissue, as well as a diffuse increase in reticulum.

The following is a typical case history.

L. D., an 11-year-old white girl, was first admitted to the Children's Medical Center because of splenomegaly, anemia, and weight loss. Past history revealed that one year prior to admission she was noted to be pale and weak. Three months prior to admission, she was irritable and fatigued and had a poor appetite. Because of this she was admitted to another hospital, where a greatly enlarged spleen was noted. There had been no past history of jaundice.

Physical examination showed the patient to be well developed, but pale and poorly nourished. The liver was 2 cm. below the costal margin, and the spleen was 8 cm. below the costal margin.

The blood hemoglobin was 9.0 mg. per 100 cc., the white cell count 8300, and the platelets normal. The guaiac test on the stool was positive on two occasions. Barium swallow revealed esophageal varices. The thymol turbidity test was 10.0 units, thymol flocculation 3+ to 4+, cephalin-cholesterol flocculation 4+, one-minute bilirubin 0.86 mg. per 100 cc., total bilirubin 1.1 gm. Febrile agglutinations and heterophile were negative.

A diagnosis of cirrhosis of the liver with esophageal varices was made. Because of her poor general condition, she was sent to a convalescent home for rehabilitation. Three months after admission, a splenectomy and splenorenal shunt were performed. A biopsy of the liver was done at the same time. Convalescence was uneventful.

She has been followed in the outpatient department for the past two years. She has been entirely well and free from symptoms. Her appetite and energy have both improved. Physical examination shows the liver to be no longer palpable. The thymol turbidity test was 20.0 units, thymol flocculation 3+, cephalin-cholesterol flocculation 3+, one-minute bilirubin 0.32 mg. per 100 cc. and total bilirubin 0.90 mg.

The biopsy specimen of the liver (Fig. 6) revealed a complete distortion of the lobular pattern with large areas of regenerated liver substance. Inflammatory changes were present only at the border of the lobules and the portal triads. The spleen was five times the normal weight and had a slight increase in the density of the fibrous and reticulum pattern.

Comment.—The liver sections in all the patients showed active hepatitis and postnecrotic scarring. The etiology for this is as yet unclear. Some pathologists have attributed these changes to toxins[83] or infections.[32] Although these may be significant in one or two cases, it would be inconceivable that all these patients had received the same insult. The postnecrotic scarring could represent intermittent liver damage caused by viral hepatitis without icterus, which has been shown to occur with fairly great frequency.¶ Although this is an attractive hypothesis, it cannot be confirmed without an adequate method for determining past infection from hepatitis virus. The familial history, both in the present series and in previous reports,# makes one wonder if certain individuals are genetically more predisposed to this condition than others. Regardless of the etiology, it appears that the outlook for this group is considerably better than that of the two previous groups. In this series, five of the patients are still alive, and, in retrospect, three others might have been improved had splenorenal shunts been performed early in the course of the disease.

¶ References 80 and 81.

References 81-89.

2. OBSTRUCTIVE CIRRHOSIS

Sixty of the patients developed cirrhosis of the liver due to biliary obstruction. The cases were divided into three separate groups: (*a*) congenital atresia of the extrahepatic bile ducts, (*b*) other obstructions of the extrahepatic bile ducts, and (*c*) intrahepatic biliary obstruction in patients with cystic fibrosis of the pancreas.

A. BILIARY ATRESIA

Clinical Description.—Forty-nine of the infants had atresia of the extrahepatic bile ducts. Of these, 1 was treated successfully by surgical anastomosis, 4 were lost sight of, and 39 died during the first year of life. Although all showed some degree of obstructive cirrhosis pathologically, the disease process had not continued long enough to cause many of the clinical sequelae of cirrhosis.

The remaining five infants survived from 21 months to 5 years of age, and all showed the usual characteristics of cirrhosis, including hepatomegaly, splenomegaly, ascites, and varices. Although the flocculation tests for liver function were negative early in life, all five showed positive tests as they grew older and the cirrhosis progressed. Four of the patients died from bleeding esophageal varices. The fifth patient has not been followed since she was 28 months of age, and at that time she was markedly jaundiced and had ascites.

Pathology.—In the group of 49 children with obstructive cirrhosis, surgical or postmortem liver tissue was obtained in 47 cases. The livers were almost uniformly enlarged, there being only two exceptions to this finding. The degree of enlargement did not correlate with the duration of life as one might expect; the two livers having the greatest degree of enlargement (nearly four times normal) were from patients 3 months and $2\frac{5}{12}$ years old at death, respectively, and the case with the greatest shrinkage (about one-half normal) was from a patient 7 months of age at death. In children dying before 5 months of age, with a few exceptions, no significant degree of nodularity of the liver capsule or of its cut surface was discernible, but from that time on a gradually increasing coarseness of the lobules was present, with an accompanying increase in the breadth of the fibrotic perilobular tissue. All the livers were dark green or yellow on the surface. The microscopic picture showed an increasing encroachment on the parenchymal lobules from the periphery by the proliferation of bile ducts, the increasing fibrosis, and the inflammatory reaction. The major lobular patterns persisted in cases up to 2 years of age, and it was only after this that true regenerative patterns with displacement of the central veins and loss of the liver-cell cords were found. The lobules were gradually isolated and their edges rounded by the encroaching portal triads. The liver-cell cords became distorted much earlier and were markedly so as early as 3-4 months of age, the distortion being due to irregularities in cell size, and to swelling of the Kupffer cells. Multinucleate giant cells were present in about one-third of the cases of biliary atresia; these tended to give marked distortion of the liver-cell cords. Actual necrobiosis of liver cells was uncommon, although in a few cases terminal central necrosis was observed at autopsy. The periportal fibrous tissue was notable for the great irregularity of its deposition as well as the irregularity in the rapidity of its increase, there being only the roughest correlations with the duration of life. Similarly, the portal infiltrate, which consisted chiefly of lymphocytes, mononuclears, and, more rarely, polymorphonuclear cells, only rarely correlated with the width of the portal triad or with duration of life. The increase in bile ducts did not appear to be correlated with duration of life, either, and many livers from infants dying at 3-8 months had many more ducts than those from infants dying at 7 or more months. There appeared to be a definite tendency for the ducts in the center of the triads to disappear and new ducts to form at the periphery of the lobules. Indeed, in some of the cases with longer durations of life, it became difficult to identify bile ducts in many lobules, giving the suggestive appearance of an absence of the intrahepatic ducts. Occasionally, older whole lobules appeared to consist of nothing but

proliferated ducts. Bile stasis was a prominent feature in all the cases of obstructive cirrhosis and almost without exception was present in the ducts and portal triads. In the bile canaliculi the bile plugs were often placed nearer the center of the lobule than the periphery. The formation of large lakes of bile, as is seen in obstructive jaundice in the adult, was unusual. Observable stasis in the cytoplasm of liver cells was present in only half the cases and in Kupffer cells only when there was bile present in the liver cells. In about one-third of the 33 autopsied cases ascites was present in a significant degree, and in 4 of these, as noted above, there were esophageal varices demonstrated at postmortem examination. In only 13 of the autopsied cases the spleens were not significantly enlarged, but all of these were under 3 months of age. The spleens in the older infants ranged up to 12 times the normal weight, but only 10 of the 33 coming to autopsy had any discernible splenic fibrosis. Yet it appears from these figures that some degree of cirrhotic portal obstruction was present to a mild degree pathologically.

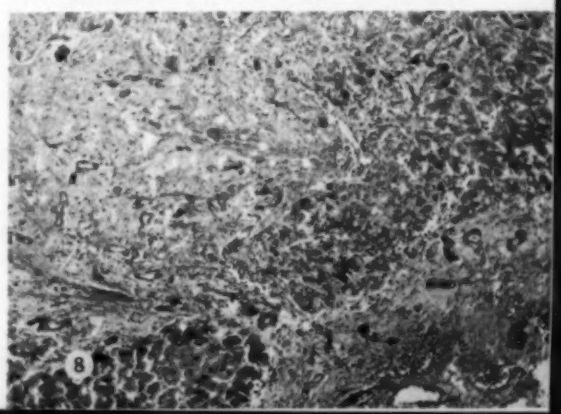
The following case is representative of those surviving beyond the first few months of life.

This child (M. C.) died at the age of 5½ years. She was said to have been jaundiced at birth. At discharge from the maternity hospital jaundice was still present, and arrangements were made for an evaluation at one month of age. At that time an exploratory laparotomy revealed an absence of the extrahepatic bile ducts. She remained jaundiced and continued to pass clay-colored stools. At 17 months of age she developed pneumonia and hematemesis and melena. At 28 months of age she was again admitted because of melena; at this time she was deeply icteric, with olive skin, a distended abdomen, and a liver extending 7-8 cm. and a spleen 6 cm. below the costal margin. The serum one-minute bilirubin determinations were 8.5 mg. per 100 cc., and total 14.9 mg.; the flocculation tests were normal. At 2⅔ years her liver reached 14 cm. and the spleen 8.0 cm. below the costal margin. She had marked ascites. The serum albumin was 2.4 gm. per 100 cc., the globulin 2.8 gm., and the sulfobromophthalien retention was 18% at 45 minutes. As on the previous admissions, transfusions were given to correct her anemia. At 2 11/12 years the thymol flocculation test was 3+-4+, thymol turbidity 10 units, and cephalin flocculation 3+-4+, and the total serum bilirubin had risen to 27.9 mg. per 100 cc. At 3¼ years she was noted to be severely retarded mentally as well as physically and had definite clubbing of the fingers and toes and markedly carious teeth. During the next year she was hospitalized several times because of acute diarrhea and anemia. At 4¼ years the prothrombin level had dropped to 18% of normal. At 4 5/12 years repeated paracenteses were required to relieve respiratory distress. Serum albumin was 1.75 gm. per 100 cc., globulin 3.76 gm. In the two weeks prior to death the patient had two syncopal attacks with prolonged atrioventricular conduction time on electrocardiogram and a low blood pressure. The final, and 22d, hospital admission was for melena and anemia. The liver and spleen had receded somewhat and were 7 and 8 cm., respectively, below the costal margin and very firm. She died quietly while asleep, without evidence of massive hemorrhage.

Fig. 7.—Biliary cirrhosis secondary to biliary atresia.

At autopsy this child was malnourished, icteric, and edematous and had a large umbilical hernia. She had ascites (600 ml.), and the liver was slightly enlarged and finely nodular (Fig. 7). The usual lobular pattern was completely destroyed (Fig. 8), often only congeries of bile ducts remaining. Many lobules were separated by fibrous sheets of great breadth. Bile stasis was present in the lobules and in the portal fibrous tissue. The kidneys and the spleen were 2 and 10 times the normal weight.

Fig. 8.—Same case at Fig. 7. Far-advanced biliary cirrhosis. Note the broad densely fibrotic portal areas; reduced ⅓ from mag. × 140. Hematoxylin and eosin.



Comment.—With the advent of modern antibacterial chemotherapy it is probable that many of these children will survive beyond the average period of four months given by earlier writers,[35] and that with the longer duration of life portal obstruction and gastrointestinal bleeding will be more important factors in their medical management. Biopsy of the liver during biliary exploration is a valuable adjunct to diagnosis, for in at least one case in which a clinical diagnosis of atresia was made and no extrahepatic bile ducts were demonstrated by the surgeon, microscopic examination revealed hepatic changes inconsistent with atresia, and bile ducts were later demonstrated at a second exploration.

B. Other Obstructions of the Bile Ducts

Clinical Description.—Five of the children had obstructions of the extrahepatic bile ducts. Two had choledochal cysts.[89] One of these was successfully repaired surgically, and the child subsequently made an uneventful recovery. The other had far-advanced cirrhosis, with marked hepatomegaly, splenomegaly, ascites, and varices. She died of liver failure within one year after the onset of jaundice. Two of the children had tumors obstructing the intrahepatic or extrahepatic ducts. All showed evidence of obstructive jaundice, and one showed marked abdominal distention and ascites. All died within one year after the onset of jaundice, despite surgical and x-ray therapy. Finally, one patient had a traumatic interruption of the common duct. This was repaired surgically by suturing and performing a cholecystoduodenostomy. Although she improved after the operation, cirrhosis and ascites developed seven years later, and she died from bleeding esophageal varices two years after that. The liver-function tests were within normal limits in all the patients in this group.

Pathology.—The livers in this group were similar to those in the biliary atresia group, with two variations in two of the cases. These were the much greater distortion of the lobular and liver-cell cords in the acquired obstructive cases. This was not, as might be expected, associated with a greater degree of inflammatory change.

A description of the fatal case of choledochal cyst follows:

This 6-year-old girl was said to have been well until one year prior to admission. At that time an increase in the size of the abdomen was noted. Despite repeated medical examinations, nothing abnormal was found until two months prior to admission, when an abdominal mass was felt. One month before admission she began to suffer fatigue, anorexia, and abdominal pain. She became pale, passed tarry stools, and had a hematemesis. On admission to the hospital she was seen to be very ill, with marked wasting, fluctuating icterus, ascites, and hepatosplenomegaly. A firm, discrete, tender mass was felt in the right midabdomen. Esophageal varices were demonstrated by roentgenogram. The laboratory studies revealed the presence of a normochromic, normocytic anemia, and the bone marrow showed erythroid hyperplasia. The liver-function studies gave values for total serum bilirubin between 6 and 30 mg. per 100 cc. with a 50 mg. one-minute reading, cephalin flocculation tests 1+, thymol turbidity 1.0. The stools were clay-colored but occasionally contained bile. The urine intermittently contained bile but was otherwise normal. A diagnostic paracentesis yielded 300 ml. of fluid from which a cell block was prepared that was interpreted as containing malignant cells. Because of this finding, the poor condition of the patient, and the precipitant terminal course, no abdominal exploration was performed. She died in hepatic coma two weeks after admission.

Fig. 9.—Biliary cirrhosis secondary to obstruction due to a choledochal cyst.

At autopsy the liver was moderately atrophic (Fig. 9) and secondary evidence of portal hyper-

tension was seen in the ascites, the enlarged spleen, and the dilatation of the superficial abdominal veins. Microscopically, a severe biliary cirrhosis was present, with broad portal triads containing many proliferated bile ducts.

Comment.—The rarity of chronic inflammation in the gall bladder and subsequent cholelithiasis in the pediatric age group reduces the importance of acquired obstruction of the common duct in the development of biliary cirrhosis to a small portion of that seen in the adult.

C. Fibrosis of the Pancreas

Clinical Description.—Seven children with fibrosis of the pancreas were found to have obstructive biliary cirrhosis at postmortem examination. All of them showed typical signs of the disease, with a history of repeated respiratory infections and an absence of trypsin in the duodenal secretions when tested. Four of the seven patients had easily palpable livers, and one developed jaundice shortly before death. In only one of the cases was the liver a significant factor as a cause of the death of the child. In this case the albumin was exceptionally low and then was associated with edema and ascites. Ascites, varices, and liver failure were not usually a part of the disease process. In but one of the seven children was significant liver damage suspected before death. Liver-function tests were negative in three children on whom they were performed.

Pathology.—The livers in this group with the exception of the case detailed below showed focal lesions for the most part and were of normal weight. The lobular pattern was grossly distorted in many areas, but in intervening zones it was normal. In the involved areas congeries of proliferated small bile ducts were present, filling whole low-power microscopic fields. These were distended with large opaque bile plugs. The stasis did not extend to either the largest ducts, the canaliculi, or the liver cells. Considerable fat was present in the liver cells, but the liver cells were not distorted. The periductal areas contained a considerable number of lymphocytes and polymorphonuclear cells. The spleens were rarely (two of seven) significantly enlarged. None showed a pathologic change secondary to the liver lesions.

The following case is illustrative of this condition.

A diagnosis of fibrosis of the pancreas was first made in this 10½-year-old girl at the age of 4½ years. The patient did fairly well over the succeeding years on antibiotics and aerosol administration, although she had always refused pancreatin. Her appetite, which had been voracious during the early part of her life, decreased in the last few months. Ten days before death she developed tachypnea, chest pain, anorexia, and fatigue. One week before admission she was placed on chlortetracycline (Aureomycin) and erythromycin therapy. On admission she was in severe respiratory distress, with widespread rales heard in the chest. The liver and spleen were greatly enlarged. A throat culture was positive for Pseudomonas aeruginosa. Her terminal course was rapid, and death ensued in severe respiratory distress.

At autopsy the patient was poorly nourished and developed. She had marked increase in the anteroposterior diameter of the chest. The periumbilical vessels were prominent and dilated. The lungs were very emphysematous and were covered with fibrous and fibrinous adhesions. The bronchi were dilated and the seat of bronchiectatic abscesses. Marked pulmonary fibrosis was present. There were large hilar and tracheal lymph nodes. The liver was much enlarged, weighing 1180 gm. (normal, 880 gm.) (Fig. 10). It was grossly distorted, with very unevenly arranged large, smooth, green-yellow nodules interspersed with deep fissures of shrunken connective tissue. The large liver nodules were 1-3 cm. in diameter. On cut surface broad irregular strands of connective tissue were deeply bile-stained. Microscopically, there were regenerated lobules which were heavily and diffusely infiltrated with an abundant amount of fat (Fig. 11). No necrosis of hepatic cells was evident. The portal triads varied greatly in appearance from lobule to lobule. In some areas no increase in the triads was found, and here the bile ducts were normal in number and appearance. In other areas, the portal triads were greatly condensed to 5-10 times a normal width. There was tremendous proliferation of the bile ducts, and each enlarged, dilated duct contained a broad opaque mass of bile that distended the duct. No bile stasis was noted away from the small ducts of the triads; the larger excretory ducts were free of bile plugs. Inflammatory cells were present in the portal triads. These were chiefly lymphocytes and polymorphonuclear cells. A few inflammatory cells were present in the small bile ducts themselves. The spleen was enlarged by

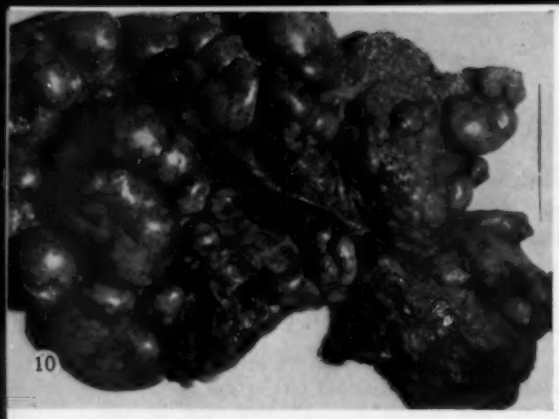
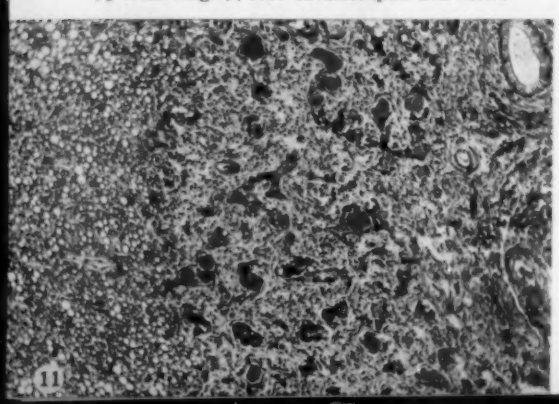


Fig. 10.—Cirrhosis secondary to pancreatic fibrosis.

one-half its normal weight; it was congested, but no fibrosis or increase in the reticulum was present. The pancreas was atrophic to an extreme degree, the few remaining ducts and acini being distended with opaque plugs of inspissated secretion. Hemorrhoids were noted but no esophageal varices. The lung cultures were positive for Friedländer's bacillus, P. aeruginosa, and Streptococcus pyogenes.

Comment.—Farber [39] has suggested that this cirrhosis appears to be secondary to intrahepatic biliary obstruction, since the dilated small bile ducts are filled with a thick inspissated eosinophilic material resembling that found in the pancreatic ducts of the same patients. The inspissation of the mucoproteins in some of the finer intrahepatic bile ducts leads to their obstruction, dilatation, and proliferation. Secondary inflammation of the ductal or periductal structures may take place. The obstructive bile plugs in the smaller bile ducts are regarded as being another manifestation of the altered activity of the mucus-producing and other exocrine glands of the lungs, alimentary tract, and pancreas in cases of fibrosis of the pancreas. The age distribution of the children with cirrhosis in cystic pancreatic fibrosis varied from 5½ months to 10½ years, yet it may be of more significance that three of four of the cases dying after 6 years of age had cirrhotic lesions. This agrees with Bodian's [40] observation that while proliferation of the bile ducts may be seen very early, fibrosis in the portal triads becomes increasingly prominent after one year of age. We do not find the high incidence of these focal lesions in the liver of the case that Bodian reports.

Fig. 11.—Same case as Fig. 10. The lobules contain much fat; the proliferated bile ducts are distended and contain opaque bile plugs; reduced ⅓ from mag. × 100. Hematoxylin and eosin.



The 7 cases presented here were obtained from a total of 160 cases of cystic fibrosis of the pancreas examined at autopsy. Though varying degrees of fatty infiltration were found at autopsy in pancreatic fibrosis in cases in which nutrition is poor, we have not observed any cases with nutritional cirrhosis. We do not believe the focal biliary cirrhosis described here is secondary to malnutrition as suggested by Webster and Williams [41] although the development of such alterations in the liver might be expected from the experience of Chaikoff and co-workers [90] with depancreatized dogs.

3. CIRRHOSIS OF THE LIVER DUE TO MISCELLANEOUS CAUSES

Seven children developed cirrhosis of the liver due to miscellaneous causes. Two of the patients had glycogen-storage disease of an unusual type, two had galactosemia, one had cardiac cirrhosis of the liver associated with coarctation of the aorta and idiopathic medial hypertrophy of the pulmonary arterioles, one had cirrhosis associated with cholangitis, and one had cirrhosis secondary to hemosiderosis arising from repeated transfusions in a patient with aplastic anemia.

Example cases are given below.

A. Glycogen-Storage Disease

The patient was born after a normal pregnancy and uneventful delivery. The early infancy was not remarkable, but at 8 months of age the abdomen gradually increased in size and the patient became anemic. On admission to the hospital at 1⅝ years, the infant was well developed and nourished, but the liver extended 12 cm. below the right and the spleen 9 cm. below the left costal margin. The urine had 0+-1+ albumin, 0+-1+ sugar and no cellular elements. There was an anemia of 7.2 gm. per 100 cc. and a leucocyte count of

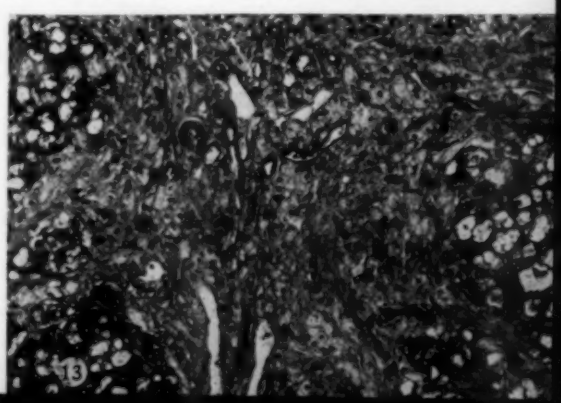
2800, with a normal differential count. The blood chemical values were normal except for an increase in the free cholesterol portion to 47% of the total 163 mg. per 100 cc. and an elevated blood glycogen to 9.5 mg. per 100 cc. (normal 5-6 mg.). Epinephrine- and glucose-tolerance curves were normal. The thymol turbidity test was 4.2, thymol flocculation 3+-4+, cephalin flocculation 3+, with normal bilirubin values. Bone-marrow aspirations were within normal limits. A splenectomy, lymph node and liver biopsy, and gall-bladder removal were performed. The spleen was greatly enlarged, 285 gm. in weight (normal, 33 gm.), and had features of congestive splenomegaly, as well as many foam cells in the sinusoids, which stained patchily for glycogen. Similar cells were present in the lymph node. The liver was cirrhotic with many large foam cells, having enormous opaque refractile vacuoles in the portal areas and sinusoids. Large amounts of glycogen were present in the liver cells in large opaque vacuoles. After splenectomy the leucocyte, platelet, and erythrocyte counts and the hemoglobin level rose to normal. The child was discharged and remained fairly well for one month, when she again entered the hospital for investigation. While in the hospital she developed an otitis media, fever, tachycardia, and increased respiratory rate. The lungs were clear, but the heart was enlarged, and the neck veins were distended. An electrocardiogram showed low T waves. Increasing cardiac distress developed, and death ensued.

At autopsy the infant was well developed and well nourished. The skin had a faint pigmentation, more consistent with carotenemia than icterus. The abdomen was protuberant. The pericardial cavity was distended with 160 ml. of turbid yellow fluid, and the entire visceral pericardium was coated with a creamy gray gelatinous exudate, which was sterile on culture and contained no organism on smear. The heart was twice the normal weight, but was not unusual in outline. Microscopically, there was an acute fibrinous organizing pericarditis and a mild myocardial hypertrophy. No abnormal vacuolation of the muscle fibers was present. The lungs were atelectatic and edematous, with focal areas of proliferated alveolar macrophages. In the intestinal lamina propria large pale mononuclear cells as described under the liver were found. The liver weighed 1980 gm. (normal, 384 gm.) (Fig. 12); it was normal in shape but firm in consistency and pale yellow in color. The lobular pattern was greatly increased in prominence, with the centers standing out above the fibrotic interlobular septa. On cut section the same appearance was present, and the surface of the liver had an almost ivory appearance. The duct system was patent. Microscopically, the liver displayed a very marked distortion of the lobular and interlobular pattern,

Fig. 12.—Cirrhosis in association with glycogen-storage disease of the liver. Note also the distended pericardial sac, secondary to a pericardial effusion.

with isolation of small lobules and frequently of individual liver cells by dense collagen bands (Fig. 13). In the interstices of the collagenous bands were many foam cells with a light blue, finely vacuolate cytoplasm. Similar cells were also seen in the liver sinusoids. The liver cells showed much distortion and contained large distorting vacuoles with an almost crystallized refractile material in them. No significant inflammation was present. The foam cells of both the hepatic framework and the parenchyma stained heavily for glycogen, but no lipid was demonstrable. The parenchymal cells but not the macrophages gave a positive reaction with Hale's mucopolysaccharide stain and a purple reaction with iodine. No bile stasis was present in the liver. The peripancreatic and periportal lymph nodes were enlarged (up to 3.5 cm.) and yellow-brown. Foam cells having a positive reaction for glycogen were present in the lymph sinusoids. Similar cells were found among lymphocytic collections in the interstitium of the kidneys as well

Fig. 13.—Same case as Fig. 12. Note the vacuoles in the parenchymal cells and the storage cells in the interstices of the broad portal triads; glycogen was present in both these areas; reduced ⅓ from mag. × 225. Mallory's aniline blue stain.



as in the bone marrow and thymus gland. No abnormalities of the brain were recognized. Death was believed to be due to pericarditis and heart failure. A younger male sibling is known to have similar complaints of pericarditis and greatly enlarged liver and spleen.

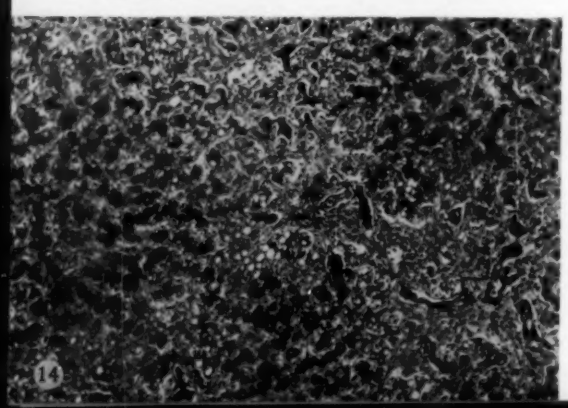
Comment.—These cases are distinct from the classical cases of von Gierke's glycogen-storage disease associated with lipemia, fatty deposition in the liver, and enlargement of the kidneys due to glycogen and fatty deposition. The latter do not usually show a cirrhosis. In these two cases and in those of Andersen,[67] the stored glycogen was abnormal and had some of the properties of starch.

B. Galactosemia

This infant was the product of the first pregnancy and had healthy parents. The family history is of interest in that the paternal great-uncle died of "sugar diabetes." The delivery was uneventful, but following delivery the infant was listless and dehydrated, and nursed with difficulty. His discharge weight was 1 oz. above birth weight. At 18 days of age projectile vomiting and diarrhea began. At 32 days of age the abdomen had become distended, with a "blue ring about the navel." At 39 days of age much free fluid was present in the abdomen, with an umbilical hernia and abdominal venous engorgement. The child was admitted to another hospital. Sugar (2%) was present in the urine, as well as albumin. At 43 days of age pitting edema was present in the lower extremities. After removal of 250 ml. of ascitic fluid the liver was palpable 5 cm. below the costal margin. The urine contained sugar and albumin. The leucocyte count was elevated to 53,950 but subsequently fell to within normal limits. The total protein was 2.4 gm. per 100 cc. No antemortem blood sugar determination was carried out. One of two urine specimens was reported as containing no sugar, but this was during a period of low milk intake and vigorous intravenous therapy with dextrose solution. Repeated injections of salt-poor albumin were given to improve the plasma protein level and to replace protein removed by the repeated abdominal paracenteses. Because of poor food intake, 5½ oz. per 24 hours, dextrose and protein hydrolysate (Amigen) solutions were given regularly to combat continued dehydration. Jaundice appeared on the sixth hospital day and increased steadily. A sulfobromophthalein test revealed a 44% retention in 10 minutes. In spite of supportive therapy the child's condition continued to regress, and she died on the 19th hospital day.

At autopsy the infant was small and poorly nourished, with a marked generalized jaundice. The abdomen was distended, and the superficial vessels were dilated. There was a confluent bronchopneumonia of the right middle and lower lobes of the lungs. There was 50 ml. of fluid in the peritoneal cavity. The bile ducts and gall bladder were anatomically normal and contained bile. The spleen was twice normal weight and microscopically was congested, with a slight increase in polymorphonuclear cells in the red pulp. The liver was not over the usual weight but had a finely granular pattern, the depressed areas being green and the 1-2 mm. nodules being tan-colored. It was very firm and cut with a grating sensation. The gross lobular pattern was maintained but accentuated. Microscopically, the liver showed marked shrinkage of the lobules due to loss of parenchymal cells (Fig. 14). The liver cells did not appear shrunken, but the liver-cell cords were disturbed. Numerous bile casts were present in the canaliculi, and the nuclei of the parenchymal cells were displaced to the edge of the cell away from the bile canaliculus. Little fat was present, but this was laid down next to the bile canaliculus. The liver-cell cords displayed thus the characteristic "acinar" pattern seen in galactosemia. No inflammation was noted in the the lobules. The portal triads were greatly enlarged by fibrous tissue and by the presence of many proliferated bile ducts. Here again no significant degree of inflammation was present. A small amount of thin bile was present in a few of the bile ducts. None of them were dilated. The remainder of the pathological examination was unremarkable except for enlargement of and bile deposits in the kidneys.

Fig. 14.—Cirrhosis in association with galactosemia; reduced ⅓ from mag. × 140. Hematoxylin and eosin.



Comment.—Three other children coming to autopsy with a proved diagnosis of galactosemia in the first few weeks of life had only minimal increases in the width of the portal triads and could not be considered to have cirrhosis.

C. Cardiac Cirrhosis

This one-month-old infant was admitted to the hospital because of dyspnea and cyanosis for two

and one-half days. The first such attack had occurred at the age of 14 days; several attacks had followed, one of which required hospitalization and treatment with oxygen. On admission, shortly before death, the respirations were very rapid, cyanosis increased with crying, and marked retraction of the ribs was present on inspiration. The heart was greatly enlarged; a poorly defined continuous murmur was present. The liver was palpable at the umbilicus and the spleen 2 cm. below the costal margin. The heart was about twice the normal size, with dilatation and hypertrophy of the right side of the heart being most prominent. A fetal type coarctation of the aorta was present proximal to the closing ductus arteriosus. The pulmonary artery was thickened on gross examination, even within the lung parenchyma, and measurements on ratio of lumens to walls in small pulmonary vessels showed an unusually high number of small lumens and thick walls. The liver was slightly enlarged. The liver grossly displayed the sharp demarcation between right and left lobes due to increased fatty change and decreased vascularity often seen in livers of the newborn. Microscopically, the liver showed a well-advanced cardiac cirrhosis with central fibrosis and reversed lobular patterns which are found in the advanced cardiac cirrhosis of the adult (Fig. 15). This change was marked on the side of the decreased fat but minimal on the right lobe, where marked fatty metamorphosis was present.

Comment.—Cardiac cirrhosis appears to be an unusual finding in congenital heart disease despite the often long-continued cardiac failure and severe passive congestion of the liver. The case cited above is thus doubly unusual because of the nature of the cardiac disease and the short duration of the disease. Cardiac cirrhosis is also infrequent in the children who die of rheumatic heart disease, none being present in our autopsy series of over 30 cases.

D. Cirrhosis Associated with Cholangitis

This patient had cirrhosis of the liver associated with cholangitis. This was preceded by jaundice, clay-colored stools, and poor weight gain and clinically could not have been differentiated from neonatal hepatitis. Unfortunately, a biopsy of the liver was not done during the acute stage of the disease. At 4 months of age, the patient developed intestinal obstruction due to adhesions. The patient was, therefore, reexplored, and death from cholangitis occurred during the postoperative period.

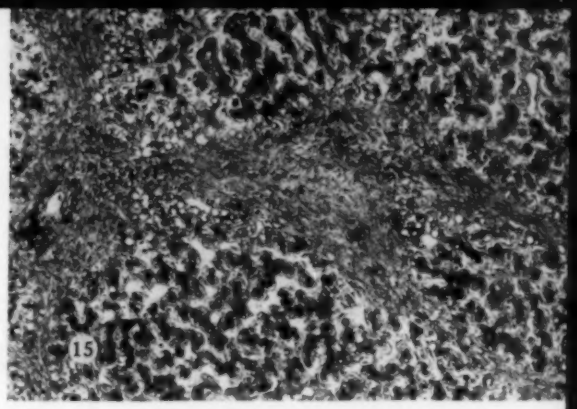


Fig. 15.—Cardiac cirrhosis. The fibrotic bands connect the central veins of adjacent lobules; reduced ⅓ from mag. × 155. Hematoxylin and eosin.

This infant was born after a normal full-term pregnancy and delivery. One sibling is living and well. The stools were clay-colored shortly after the infant's discharge from the hospital where he was born, but they subsequently again became yellow. The urine had been dark from the first few days of life. At 5 weeks of age jaundice was first noted at a medical check-up; it persisted but fluctuated until 8 weeks of age, when the child was admitted to the Children's Medical Center. Then the infant was jaundiced and undernourished. The liver was 4.0 cm. below the costal margin and was firm and smooth. The spleen came 2.0 cm. below the costal margin. The stools were free from bile. The urine contained 1+ bile, and the serum bilirubin determinations were 4.0 mg. per 100 cc. at one minute, with a total of 7.0 mg. The liver flocculation tests and total protein levels were normal. The Hinton reaction was negative. An exploratory operation revealed a normal extrahepatic biliary tree with bile present in the gall bladder. After operation the jaundice began to fade, and bile appeared in the stools. A mild bout of ileus developed but subsequently subsided. A few days after discharge the patient developed cough and diarrhea; his jaundice, dark urine, and light-colored stools persisted. The physical findings remained the same as on the first admission. Diarrhea became increasingly severe. Finally the obstructive vomiting developed along with an absence of peristaltic signs. A second operation for lysis of adhesions was performed, but the patient died soon after operation, at 4 months of age. No significant change in liver-function tests accompanied this terminal illness.

At postmortem examination the infant was icteric. The lungs were congested. There was 75 ml. of bloody fluid in the peritoneal cavity from which an alpha-hemolytic Streptococcus and Escherichia coli were cultured. These organisms were also cultured from the right pleural cavity and both lungs. Numerous adhesions were present in the abdominal cavity; others had been recently lysed.

An acute fibrinous peritonitis was present microscopically. The periportal and peripancreatic lymph

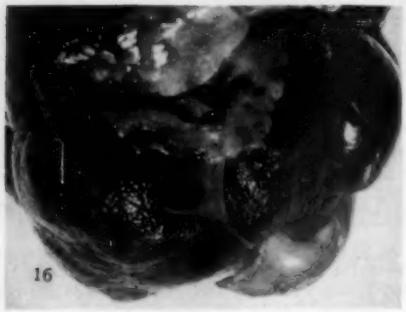


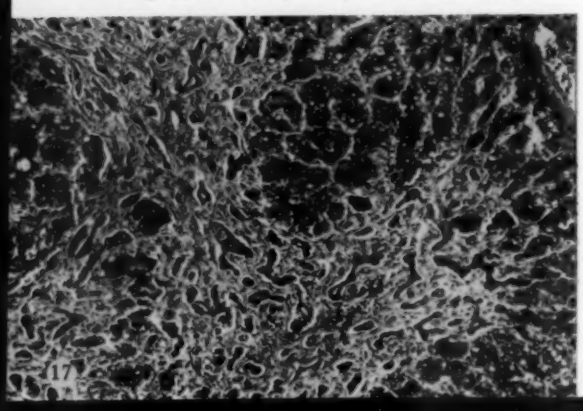
Fig. 16.—Cirrhosis associated with cholangitis.

nodes were involved with an acute inflammation. The liver extended 5.0 cm. below the costal margin and weighed 220 gm. (normal, 140 gm.) (Fig. 16). It was finely granular on the surface and cut section and was quite bile-stained. The extrahepatic ducts and gall bladder were all patent and contained bile.

The microscopic pattern of the liver lobules was maintained, though the portal triads were fibrotic and considerably widened (Fig. 17). The liver-cell cords were shrunken and bile-stained, but few necrobiotic changes were seen in the parenchymal cells. At the periphery of the lobules the parenchymal cells contained considerable fat and bile. No multinucleated giant parenchymal forms were present. Much bile stasis was present in the canaliculi. The Kupffer cells were swollen and filled with bile. Bile-filled macrophages were also present in the portal triads. The bile-duct epithelium was swollen, and there was an increased number of ducts. Occasional periductal polymorphonuclear cells were found in the portal triads. The kidneys were enlarged and contained bile casts microscopically. No other significant pathologic findings were evident.

Comment.—This case is unique in our series of cases of cirrhosis and neonatal hepatitis. The pathological findings were quite distinct and have some similarities to the findings in the livers of cases with biliary atresia. The picture fits closely the infectious cirrhosis as described by MacMahon.[91] The etiology of this hepatic lesion has been suggested to be in some cases of viral origin. Here it is thought to be more closely related to an ascending bile duct infection, as suggested by MacMahon.

Fig. 17.—Same case as Fig. 16. Marked proliferation of the bile ducts is present. Plugs are present in the canaliculi of the lobules; reduced ⅓ from mag. × 150. Phosphotungstic acid hematoxylin.



E. Cirrhosis Secondary to Hemosiderosis

This patient was first admitted to the hospital at the age of 10 weeks because of pallor; a diagnosis of hypoplastic anemia was established. The patient over the next eight and one-half years had 80 hospital admissions, during which she received nearly 200 transfusions. Her bone marrow throughout maintained its hypoplastic character. At age 7⅓ years she suffered an epidural abscess and vertebral collapse. At 8 she had a bout of congestive heart failure. At 8⅙ years a splenectomy was done in an attempt to reduce the frequency of transfusion. Death came at 8½ years, with an overwhelming pneumococcus infection of four days' duration.

The spleen, on surgical removal, was two times the normal weight and microscopically showed marked hemosiderosis with swelling and proliferation of the sinusoidal lining cells. The Malpighian follicles showed the changes of "hypersplenism," but no fibrosis of the splenic pulp was evident.

The liver at autopsy weighed 1192 gm. (normal, 852 gm.) (Fig. 18). The surface was distorted by the presence of nodules of various sizes, measuring 0.4-1.0 cm. in diameter. The liver cut with increased resistance and had the same appearance on the cut surface. Microscopically, the liver was heavily impregnated by hemosiderin both in the Kupffer cells and the parenchymal cells; large masses of pigment were present in phagocytic cells of the portal triads (Fig. 19). The latter were of variable width, some only slightly over normal in width, others were very broad and sent wide bands of connective tissue into the lobules toward the central veins, thus distorting the lobules. No regenerative nodules were recognized. A slight infiltration of lymphocytes and eosinophiles was present in the portal triads.

The kidneys were 50% overweight and had numerous tubules whose cells were heavily impregnated with hemosiderin. Massive deposits of iron were also present in the pancreas, lymph nodes, heart, and adrenal glands.

Comment.—Heavy deposits of iron may be found in the liver parenchyma and Kupffer's cells in persons to whom a large number of transfusions have been given over a period of

time.* In most instances no scarring of the liver results, or at most, only a small amount of periportal fibrosis. Regenerative nodules have not been described except in instances where some other pathological process was present. But cirrhosis has been described accompanying "transfusional siderosis." [74] In the present case, although no regenerative nodules were present, the gross scarring and the microscopic distortion of the lobules are believed sufficient to warrant a diagnosis of cirrhosis. This process is to be separated from idiopathic hemochromatosis [92] in which cirrhosis is a uniform part of the pathological picture. The latter has not been described in children.

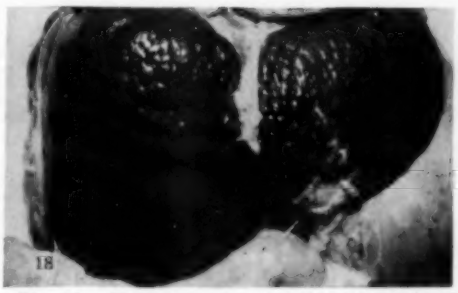


Fig. 18.—Cirrhosis secondary to transfusional siderosis.

COMMENT AND CONCLUSIONS

The present study of cirrhosis of the liver was undertaken to determine the etiology and pathogenesis of this condition among infants and young children in our hospital population. It is apparent that this disease differs greatly from cirrhosis seen in children in other parts of the world. None of the cases in the present series showed the massive hepatic necrosis described in Hindu children or the enlarged fatty livers seen among the children with kwashiorkor in Africa and the West Indies. This is not surprising in view of the fact that none of the children in the present group suffered from either protein or vitamin deficiency to any marked degree. It was interesting to note also that none of the cases showed evidence of the classical Laennec's cirrhosis, which is the commonest form of cirrhosis among adults. This may be due to the absence of alcoholism and severe nutritional disturbances in children, or it may represent a difference in response on the part of the liver in infancy and childhood. Instead of becoming damaged and replaced by fibrous tissue over a long period of years, the liver may either regenerate rapidly and completely or show rapid necrosis and degeneration without a marked regenerative process.

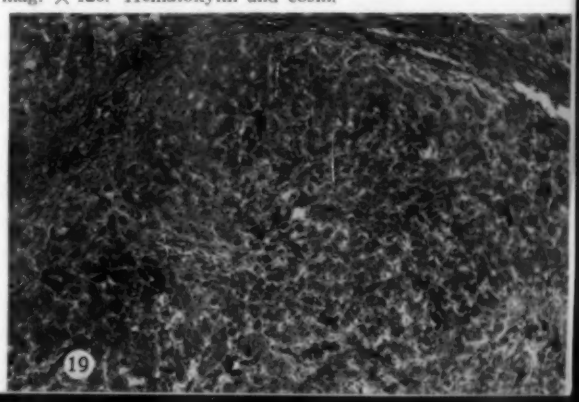
The primary causes of cirrhosis of the liver in infants and children in this part of the world are hepatitis and congenital malformations of the biliary tree. Although the latter is not unusual in a pediatric population, the frequency of cirrhosis associated with hepatitis is a surprising and important one, suggesting that the disease is not entirely benign among children. This emphasizes the importance of recognition of mild and subclinical cases without icterus and also of careful follow-up of known cases after signs and symptoms have disappeared. Yet, in view of the large numbers of patients with acute infectious hepatitis in this area before and during the period covered by this survey, it is obvious that cirrhosis is a relatively uncommon complication of hepatitis in childhood.

The diagnosis of cirrhosis in galactosemia is relatively rare. This condition, however, should always be considered in the differential diagnosis of cirrhosis of the liver in children.

Dr. Herbert Fanger, of the Rhode Island Hospital, Dr. Edward MacMahon, of the Boston Floating Hospital, Dr. Donald Brown, of the Beverly Hospital, and Dr. J. R. Bowman, of the Bowman Clinic, Johnson City, Tenn., gave permission for review of the slides on certain cases.

The photomicrographs were made by Mr. John Carabitses.

Fig. 19.—Same case as Fig. 18; reduced ⅓ from mag. × 120. Hematoxylin and eosin.



* References 71-74.

REFERENCES

1. Poynton, F. J., and Wyllie, W. G.: Hepatic Cirrhosis in Children: Biliary Forms, Arch. Dis. Childhood **1**:1, 1926.

2. Harrell, G. T., and McBryde, A.: Cirrhosis of the Liver in Children, Am. J. Dis. Child. **59**: 1301, 1940.

3. Keller, P. D., and Nute, W. L., Jr.: Cirrhosis of the Liver in Children: Clinical and Pathologic Study of 40 Cases, J. Pediat. **34**:588, 1949.

4. Ghose, J. N.: Biliary Cirrhosis of Children, Lancet **1**:321, 1895.

5. MacKenzie, E.: Biliary Cirrhosis in Children, Lancet **1**:322, 1895.

6. Pandalai, N. G.: Notes and Observations on "Infantile Biliary Cirrhosis," Indian M. Gaz. **69**:190, 1934.

7. Radhakrishna Rao, M. V.: Histopathology of the Liver in "Infantile Biliary Cirrhosis," Indian J. M. Res. **23**:69, 1935.

8. Himsworth, H. P.: Lectures on the Liver and Its Diseases, Ed. 2, Cambridge, Mass., Harvard University Press, 1950, pp. 98-101.

9. Trowell, H. C., and Davies, J. N. P.: Kwashiorkor: I. Nutritional Background, History, Distribution, and Incidence, Brit. M. J. **2**:796, 1952.

10. Trowell, H. C.; Davies, J. N. P., and Dean, R. F. A.: Kwashiorkor: II. Clinical Picture, Pathology, and Differential Diagnosis, Brit. M. J. **2**:798, 1952.

11. Gillman, J., and Gillman, T.: Perspectives in Human Malnutrition: A Contribution to the Biology of Disease from a Clinical and Pathological Study of Chronic Malnutrition and Pellagra in the African, New York, Grune & Stratton, Inc., 1951.

12. Davies, J. N. P.: The Essential Pathology of Kwashiorkor, Lancet **1**:317, 1948.

13. Waterlow, J. C.: Fatty Liver Disease in Infants in the British West Indies, Medical Research Council Special Report Series, No. 263, London, Her Majesty's Stationery Office, 1948.

14. McFarlane, A. L., and Branday, W. J.: Hepatic Enlargement with Ascites in Children, Brit. M. J. **1**:838, 1945.

15. Braid, F., and Ebbs, J. H.: Atrophic Cirrhosis of the Liver Following Icterus Gravis Neonatorum, with Pathological Report, Arch. Dis. Childhood **12**:389, 1937.

16. Hawksley, J. C., and Lightwood, R.: A Contribution to the Study of Erythroblastosis: Icterus Gravis Neonatorum, Quart. J. Med. **3**: 155, 1934.

17. Henderson, J. L.: A 4th Type of Erythroblastosis Foetalis Showing Hepatic Cirrhosis in the Macerated Foetus, Arch. Dis. Childhood **17**: 49, 1942.

18. Gilmour, J. R.: Erythroblastosis Foetalis, Arch. Dis. Childhood **19**:1, 1944.

19. Craig, J. M.: Sequences in the Development of Cirrhosis of the Liver in Cases of Erythroblastosis Fetalis, Arch. Path. **49**:665, 1950.

20. Gerrard, J. W.: Icterus Gravis and Cirrhosis of the Liver, Brit. M. J. **1**:1385, 1952.

21. Townsend, E. H., Jr.; Mason, H. H., and Strong, P. S.: Galactosemia and Its Relation to Laennec's Cirrhosis: Review of the Literature and Presentation of 6 Additional Cases, Pediatrics **7**: 760, 1951.

22. Donnell, G. N., and Lann, S. H.: Galactosemia: Report of 4 Cases, Pediatrics **7**:503, 1951.

23. Hsia, D. Y. Y.; Hsia, H. H.; Green, S.: Kay, M., and Gellis, S. S.: Amino-Aciduria in Galactosemia, A. M. A. Am. J. Dis. Child. **88**:458, 1954.

24. Dunsky, I.: Congenital Biliary Cirrhosis, Am. J. Dis. Child. **71**:150, 1946.

25. Janseen, T. A. E., and DeLange, C.: Cirrhosis of the Liver and of the Pancreas, and Disturbances of the Sugar Metabolism in an 8 Week Old Infant, Ann. pædiat. **165**:213, 1945.

26. Bain, H. W.; Sass-Kortsak, A.; Bowden, D.; Jackson, S.; Walker, N. F., and Chute, A. L.: Galactosemia, presented at the Society for Pediatric Research, Buck Hill Falls, Pa., May 6, 1954.

27. Edmonds, A. M.; Hennigar, G. R., and Crooks, R.: Galactosemia: Report of a Case with Autopsy, Pediatrics **10**:40, 1952.

28. Wilson, S. A. K.: Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver, Brain **34**: 295, 1912.

29. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944.

30. Uzman, L. L., and Hood, B.: The Familial Nature of the Amino-Aciduria of Wilson's Disease (Hepatolenticular Degeneration), Am. J. M. Sc. **223**:392, 1952.

31. Bon, H. S., and Bickel, H.: Morbid Anatomy, Histology and Pathogenesis of Lignac-Faconi Disease, Acta pædiat., Vol. 42, Supp. 90, 1953.

32. Moon, V. H.: Infection as a Cause of Juvenile Cirrhosis, Am. J. M. Sc. **177**:681, 1929.

33. Moon, V. H.: Experimental Cirrhosis in Relation to Human Cirrhosis, Arch. Pat. **18**:381, 1934.

34. Holmes, J. B.: Congenital Obliteration of the Bile Ducts: Diagnosis and Suggestions for Treatment, Am. J. Dis. Child. **11**:405, 1916.

35. MacMahon, H. E., and Mallory, F. B.: Obstructive Cirrhosis, Am. J. Path. **5**:645, 1929.

36. Ladd, W. E.: Congenital Obstruction of the Bile Ducts, Ann. Surg. **102**:742, 1935.

37. Gross, R. E.: The Surgery of Infancy and Childhood: Its Principles and Techniques, Philadelphia, W. B. Saunders Company, 1953.

38. Hsia, D. Y. Y.; Patterson, P.; Allen, F. H., Jr.; Diamond, L. K., and Gellis, S. S.: Prolonged Obstructive Jaundice in Infancy: I. A General Survey of 156 Cases, Pediatrics **10**:243, 1952.

39. Farber, S.: Pancreatic Function and Disease in Early Life: V. Pathologic Changes Associated with Pancreatic Insufficiency in Early Life, Arch. Path. **37**:238, 1944.

40. Bodian, M., Editor: Fibrocystic Disease of the Pancreas: A Congenital Disorder of Mucus Production—Mucosis, New York, Grune & Stratton, Inc., 1953, p. 244.

41. Webster, R., and Williams, H.: Hepatic Cirrhosis Associated with Fibrocystic Disease of the Pancreas: Clinical and Pathological Reports of 5 Patients, Arch. Dis. Childhood **28**:343-350, 1953.

42. Katzin, H. M.; Waller, J. V., and Blumgart, H. L.: "Cardiac Cirrhosis" of the Liver: A Clinical and Pathologic Study, Arch. Int. Med. **64**: 457, 1939.

43. Koletsky, S., and Barnebee, J. H.: "Cardiac" or Congestive Cirrhosis: Pathologic and Clinical Aspects, Am. J. M. Sc. **207**:421, 1944.

44. Kimball, S.; Chapple, W. H. C., and Sanes, S.: Jaundice in Relation to Cirrhosis of the Liver, J. A. M. A. **134**:662, 1947.

45. Howard, R., and Watson, C. J.: Antecedent Jaundice in Cirrhosis of the Liver, Arch. Int. Med. **80**:1, 1947.

46. Spellberg, M. A.: Sequelae of Acute Hepatitis, Am. Pract. **2**:311, 1948.

47. Post, J.; Gellis, S., and Lindenauer, H. J.: Studies on Sequelae of Acute Infectious Hepatitis, Ann. Int. Med. **33**:1378, 1950.

48. Koszalka, M. F.; Lindert, M. C. F.; Snodgrass, H. M., and Lerner, H. B.: Hepatitis and Its Sequelae, Including Development of Portal Cirrhosis: Observations on 100 Cases, Arch. Int. Med. **84**:782, 1949.

49. Warthin, T. A., and Dalrymple, W.: Symposium on Specific Methods of Treatment: Subacute and Chronic Hepatitis; Diagnosis and Treatment, M. Clin. North America **36**:1341, 1952.

50. Sutton, T. L.: Cirrhosis of the Liver in Childhood: Report of a Case of Atrophic Cirrhosis in a Boy Aged 10 Years, Am. J. Dis. Child. **39**:141, 1930.

51. Saffro, L. B., and Calvin, J. K.: Cirrhosis of the Liver, Am. J. Dis. Child. **42**:489, 1931.

52. Laurie, W. S.: Hepatic Cirrhosis with Splenomegaly in Children, M. J. Australia **1**:178, 1935.

53. Schindler, J. A., and Kindschi, L. G.: Juvenile Cirrhosis of the Liver in 3 Members of the Same Family, Wisconsin M. J. **50**:1004, 1951.

54. Drake, M. E.: Symposium on Pediatrics: Infectious (Epidemic) Hepatitis in Infancy and Childhood, M. Clin. North America **36**:1637, 1952.

55. Curtiss, C. C.: Juvenile Cirrhosis of the Liver, with Report of Case, Arch. Pediat. **51**:396, 1934.

56. Williams, B.: Cirrhosis of the Liver in a Baby, Brit. M. J. **1**:850, 1934.

57. Webster, R.: Pathological Reports from Children's Hospital, Melbourne: Juvenile Cirrhosis of the Liver, M. J. Australia **2**:246, 1938.

58. Hinden, E.: Hepatic Cirrhosis Following Neonatal Jaundice, Proc. Roy. Soc. Med. **42**: 560, 1949.

59. Reed, M. E.: Cirrhosis of the Liver: Report of Case in a 20-Day-Old Child, Arch. Pediat. **60**: 357, 1953.

60. Stokes, J., Jr.; Wolman, I. J.; Blanchard, M. C., and Farquhar, J. D.: Viral Hepatitis in Newborn: Clinical Features, Epidemiology, and Pathology, A. M. A. Am. J. Dis. Child. **82**:213, 1951.

61. Craig, J. M., and Landing, B. H.: Form of Hepatitis in Neonatal Period Simulating Biliary Atresia, A. M. A. Arch. Path. **54**:321, 1952.

62. Harris, R. S.: Anderson, D. H., and Day, R. L.: Obstructive Jaundice in Infants with Normal Biliary Tree, Pediatrics **13**:293, 1954.

63. Popper and Volk, in Kagan, S. R., Editor: Abraham Levinson Anniversary Volume Studies in Pediatrics and Medical History in Honor of Dr. Abraham Levinson on His Sixtieth Birthday, New York, Troben Press, Inc., 1949.

64. Gellis, S. S.; Craig, J. M., and Hsia, D. Y. Y.: Prolonged Obstructive Jaundice in Infancy: IV. Neonatal Hepatitis, A. M. A. Am. J. Dis. Child. **88**:285, 1954.

65. Kimmelstiel, P.: Über Glykogenose, Beitr. path. Anat. **91**:1, 1933.

66. Unshelm, E.: Die Glykogenkrankheit (Zugleich ein Beitrag zur Frage des hepatogenen Infantilismus), Jahrb. Kinderh. **137**:257, 1932.

67. Andersen, P. H.: Studies on Glycogen Disease with Report of a Case in Which the Glycogen Was Normal in Carbohydrate Metabolism: A Symposium, edited by V. Najjar, Baltimore, Johns Hopkins Press, 1912.

68. von Gierke, E.: Hepato-Nephromeglia glykogenica (Glykogenspeicherkrankeit der Leber und der Nieren), Beitr. path. Anat. **82**:497, 1929.

69. Bridge, E. M., and Holt, L. E., Jr.: Glycogen Storage Disease: Observations on Pathologic Physiology of 2 Cases of Hepatic Form of the Disease, J. Pediat. **27**:299, 1945.

70. Mason, H. H., and Andersen, D. H.: Glycogen Disease, Am. J. Dis. Child. **61**:795, 1941.

71. Kluckner, M. S., Jr.; Baggenstoss, A. H., and Weir, J. F.: Hemochromatosis and Transfusional Hemosiderosis, Am. J. Med. **16**:382-394, 1954.

72. Wyatt, J. P.; Mighton, H. K., and Moragues, V.: Transfusional Siderosis, Am. J. Path. **26**: 883, 1950.

73. Schwartz, S. O., and Blumenthal, S. A.: Exogenous Hemochromatosis Resulting from Blood Transfusions, Blood **3**:617, 1948.

74. Ellis, J. T.; Smith, C. H., and Schulman, I.: Fibrosis and Hemosiderosis of the Liver and Pancreas in 9 Patients with Cooley's Anemia, abstracted, Am. J. Path. **29**:578, 1953.

75. Hsia, D. Y. Y., and Gellis, S. S.: Portal Hypertension in Infants and Children, to be published.

76. Scott, R. B.; Wilkins, W., and Kesseler, A.: Viral Hepatitis in Early Infancy, Pediatrics **13**: 447, 1954.

77. Hsia, D. Y. Y., and Gellis, S. S.: Prolonged Obstructive Jaundice in Infancy: III. Liver Function Tests, A. M. A. Am. J. Dis. Child. **85**:13, 1953.

78. Leffler, R. J.: The Spleen in Hypersplenism, Am. J. Path. **28**:303, 1952.

79. Denber, H. C. B., and Leibowitz, S.: Acute Anicteric Virus Hepatitis: Report of 30 Cases, J. A. M. A. **149**:546, 1952.

80. Zimmerman, H. J., and Thomas, L. J.: Anicteric Hepatitis: Report of 9 Sporadic Cases, Am. J. M. Sc. **216**:545, 1948.

81. Howard, R. P.: Cirrhosis in Children, Am. J. M. Soc. **94**:350, 1887.

82. Jollye, F. W.: Hepatic Cirrhosis Occurring in 2 Children of the Same Family, Brit. M. J. **1**:858, 1892.

83. Ely, T.: Two Cases of Cirrhosis of the Liver in Childhood, Boston M. & S. J. **170**:542, 1914.

84. Gunn, F. D.: Familial Juvenile Cirrhosis of the Liver, Arch. Path. **1**:527, 1926.

85. Bridgemen, M. L., and Robertson, T. D.: Familial Juvenile Cirrhosis of the Liver, Am. J. Dis. Child. **43**:1155, 1932.

86. Yater, W. M., and Saccardi, W. T.: Portal Cirrhosis in 2 Children of the Same Family, M. Ann. District of Columbia **12**:264, 1943.

87. Jameson, G. M., and Savarese, L. A.: Familial Portal Cirrhosis in Young Adults, U. S. Nav. M. Bull. **45**:270, 1945.

88. Adams, F. H.; Anderson, R. C., and Richdorf, L. F.: Four Siblings with Hepatic Disease Leading to Cirrhosis, A. M. A. Am. J. Dis. Child. **84**:168, 1952.

89. Gross, R. E.: Idiopathic Dilatation of the Common Bile Ducts in Children: Review of Literature and Report of 2 Cases, J. Pediat. **3**:730, 1933.

90. Chaikoff, I. L.; Connor, C. L., and Biskind, G. R.: Fatty Infiltration and Cirrhosis of the Liver in Depancreatized Dogs Maintained with Insulin, Am. J. Path. **14**:101, 1938.

91. MacMahon, H. E.: Infectious Cirrhosis, Am. J. Path. **7**:77, 1931.

92. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935.

ACUTE NONLIPID DISSEMINATED RETICULOENDOTHELIOSIS

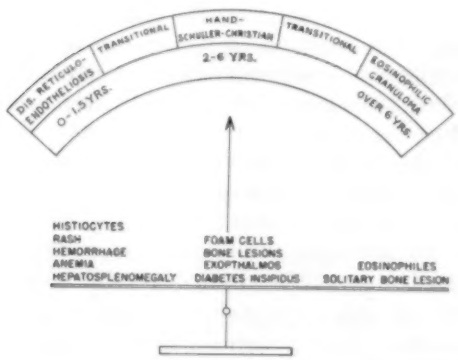
RANDOLPH BATSON, M.D.
JOHN SHAPIRO, M.D.
AMOS CHRISTIE, M.D.
and
H. D. RILEY, Jr., M.D., Nashville, Tenn.

THE NONLIPID reticuloendothelioses are usually considered to include Hand-Schüller-Christian's disease, eosinophilic granuloma of the bone, and acute disseminated reticuloendotheliosis (Letterer-Siwe's disease). The latter is the least common of this group, approximately 41 cases having been previously reported. It is the purpose of this paper to contribute to the knowledge of this disease by reviewing the literature and reporting 15 additional cases. Our patients were 13 months or younger at the onset of the disease and illustrated classical features of acute disseminated reticuloendotheliosis. These characteristics included hepatosplenomegaly, anemia, skin lesions, adenopathy, bone lesions, and recurring secondary infections. With one exception all diagnoses were confirmed pathologically.

Submitted for publication May 12, 1955.

Fellow of the National Foundation for Infantile Paralysis (Dr. Riley).

From the Departments of Pediatrics and Pathology, Vanderbilt University School of Medicine.



DISEASE SPECTRUM of NON-LIPID RETICULOENDOTHELIOSIS

Fig. 1.

HISTORICAL REVIEW

The earliest reports of nonlipid reticuloendotheliosis concerned Hand-Schüller-Christian's disease. These were by Smith,[2] Hand,[3] Kay,[4] Schüller [5] and Christian [6] and resulted in characterization of the disease as a triad consisting of diabetes insipidus, exophthalmos, and defects in membranous bones. Epstein [9] initially suggested that the triad was not necessarily always present. In 1931 Henschen [11] reviewed 57 cases of Hand-Schüller-Christian's disease pointing to the marked variability in clinical and pathological pictures. He defined eight general types, several of which did not have the classical triad of signs.

Weidman and Freeman [7] proposed that cholesterol-containing foam cells represented the essential lesion. Rowland * felt that foam cells were indicative of generalized lipid storage disease and stated that such cells developed secondary to hyperlipemia. Sosman [12] also adhered to the theory of abnormality in lipid storage, while Fraser [14] felt that the reticuloendothelial system absorbed lipid from high cholesterol levels of body fluids. Thannhauser and Magendantz,[15] noting absence of hypercholesteremia, felt that Hand-Schüller-Christian's disease was a primary xanthomatosis with high tissue lipid levels.

Interest was then focused on a related syndrome first described by Abt and Denenholz.[16] In 1931 Goldzieher and Hornick [17] accumulated 22 cases from the literature. Siwe [18] then attempted to establish a well-delineated entity with eight clinical and

* References 8 and 13.

pathologic findings which included splenomegaly, hepatomegaly, a hemorrhagic tendency, lymphadenopathy, anemia, osseous involvement, and an increase in non-lipid-containing macrophages. He felt that the disease occurrring exclusively in infants is neither hereditary nor familial.

Galeotti, Flori, and Parenti [19] in 1937 initially suggested that Hand-Schüller-Christian's and Letterer-Siwe's disease were related variants of a basic pathological process. Wallgren,[20] after reviewing 23 cases of Hand-Schüller-Christian's and Letter-Siwe's disease accumulated from the literature and his own clinic, suggested that Hand-Schüller-Christian's disease and Letterer-Siwe's disease are the results of the same fundamental process. He observed that foam cells occurred only in those cases in which the duration was three months or more and suggested that lack of foam cells in Letterer-Siwe's disease could be explained by its rapid termination with insufficient time for lipid accumulation.

In 1940 Otani and Ehrlich [21] and Lichtenstein and Jaffe [22] independently recognized and studied a process consisting of a solitary granulomatous bone lesion, the chief histologic cell of which was the eosinophile. They considered it a disorder of the reticuloendothelial system distinct from Hand-Schüller-Christian's and Letterer-Siwe's disease. Additional cases exhibiting multiple as well as solitary bone lesions appeared in the literature.† Farber [25] in 1941 reported five cases and suggested that eosinophilic granuloma of bone was still another variant of the same process present in Hand-Schüller-Christian's disease and Letterer-Siwe's disease.

Mallory [26] also looked on the three disorders as being variants of one nonlipid disease and differentiated them on the basis of patient's age, histopathology, and distribution of lesions. He commented on the occasional presence of lipid-containing cells and focal bone lesions in cases otherwise typical of Letterer-Siwe's disease. He felt that if reported cases were studied in order of chronicity every grade of transition between the three could be demonstrated. Others ‡ supported Mallory's conclusions.

Dennis and Rosahn [42] also looked on the three diseases as being related variants of the same process but felt that differences in basic pathology were the chief determinants of clinical course. Their adult case had histologic similarities to those seen in Letterer-Siwe's disease.

Some § did not agree with the concept of one basic disorder. Siwe [41] expressed the opinion that Letterer-Siwe's and Hand-Schüller-Christian's diseases are separate entities. He feels that the presence of the histiocytic stage implies Letterer-Siwe's disease, whereas fibroplastic granulation with lipoid storage is present only in the chronic process. He also believes that eosinophilic granuloma is a distinct and separate localized process. He is of the opinion that the presence of foam cells is the most significant feature of Hand-Schüller-Christian's disease and that such are not present to the same extent in the other disorders. He doubts the existence of transitional forms and feels that neither the age of the patient nor the duration of the disease influences the course.

Two patients || have been reported in which there was a single bone lesion, histologically typical of eosinophilic granuloma, but who eventually developed visceral manifestations of Letterer-Siwe's disease. The case of Freund and Ripps [39] had generalized lymphadenopathy at onset due to nonlipid reticuloendothelial hyperplasia but seven months later developed bony defects. Foot and Olcott [40] also reported skeletal involvement in the acute form of the disease. Engelbreth-Holm and co-workers [48] demonstrated the gradual progression of solitary bone lesions (eosinophilic granuloma) to Hand-Schüller-Christian's syndrome.

Steele [46] reported a case of Letterer-Siwe's disease with lipid-containing cells in the thymus and lungs, the other tissue showing nonlipid macrophages. Another patient [47]

† References 23 and 24.

‡ References 28-30 and 38.

§ References 31-34.

|| References 44 and 45.

with diabetes insipidus had a destructive femoral lesion showing areas of extensive eosinophilic infiltration and other areas of lipid-containing-histiocytic infiltration. Skin lesions have now been reported in all three disorders, and bone lesions present in all three cannot be differentiated roentgenographically. Eosinophiles are characteristically found in the bone lesions of eosinophilic granuloma, but Love and Fashena [51] also found large numbers of them in cervical lymph nodes of such a patient. Lichtenstein [56] and others [31] feel that Hand-Schüller-Christian's disease may occasionally progress rapidly and develop changes compatible with Letterer-Siwe's disease. Much has been written ¶ concerning eosinophilic granulomas with involvement of skin, lungs, and other tissues.

Since many clinical and pathological findings in Letterer-Siwe's disease are compatible with an inflammatory process, an infectious agent has long been suspected. Jaffe and Lichtenstein # feel that the three syndromes are different clinicoanatomic expressions of the same disorder resulting from a unique inflammatory reaction to some unknown infectious agent. Green and Farber [52] believed the process to be infectious but were unable to transmit the disease to laboratory animals. In 1939, Agress and Gray [49] in reporting a case of disseminated histoplasmosis concluded that the reticuloendothelial hyperplasia in this disease is quite similar to that in Letterer-Siwe's disease. Christie and co-workers [55] have discussed the differential points between acute reticuloendotheliosis and generalized histoplasmosis. No specific etiologic agent has been consistently identified, even though Samonella paratyphi B,[50] coliform organisms,* paracolon bacillus,[48] Brucella, and acid-fast organisms † have been isolated from patients with clinical pictures resembling nonlipid reticuloendotheliosis.

¶ References 29, 33, 35-37, and 55.

References 27 and 57.

* Hillman, J. W. (Nashville, Tenn.): Personal communication to the authors.

† Hartman, A. F. (St. Louis): Personal communication to the authors.

REPORT OF CASES

CASE 1 (K. S.).—This 15-month-old white boy had been in good health until five months prior to admission, when he developed anorexia, irritability, weight loss, and regression of previous developmental achievements.

Three months prior to admission, pallor, fever, and pain on passive motion appeared, and x-ray examination of the spine revealed osteolytic lesions. Six weeks prior to admission he developed a generalized maculopapular rash and an increased number of bone lesions. Lymph-node biopsy revealed changes compatible with "Hand-Schüller-Christian's disease."

On admission to Vanderbilt University Hospital, the child was irritable, febrile, lethargic, pale, and emaciated. A hemorrhagic, scaly, maculopapular rash was present in addition to hepatosplenomegaly, lymphadenopathy, and anemia. Roentgenograms revealed destructive lesions in the skull, extremities, ribs, and spine and extensive pulmonary infiltration. On supporative treatment, the child had progression of his disease, dying shortly after admission to the hospital.

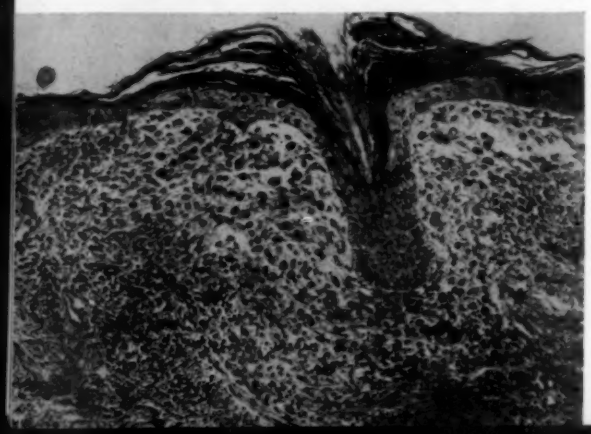
Autopsy.—The body was icteric and emaciated, with lymphadenopathy involving cervical, axillary, inguinal, mesenteric, and, to a less extent, hilar lymph nodes. These were discrete, firm, and brown on section. A generalized papular hemorrhagic rash was present. Nodules in one rib and in the sternum were yellow and gelatinous on cross section. Petechial hemorrhages were present on several serosal and mucosal surfaces. The thymus was prominent and contained numerous small hemorrhages. Both lungs were heavy, showing many small yellow nodules, often in a peribronchial location. Small nodules were present in the stomach mucosa. The liver was markedly enlarged, with numerous light yellow opacities beneath the capsule and on the cut surface. The spleen was very large, with focal hemorrhagic brown nodules. All bones examined had yellow, opaque marrow.

Microscopic Examination.—Focal collections of large mononuclear cells under an intact but scaling epithelial layer characterized the skin lesions (Fig. 3). In the lung there were granulomas (Fig. 4) of varying size containing large mononuclear cells, some fibrous tissue, and giant cells with abundant pink cytoplasma and numerous round nuclei. Such lesions occurred around bronchi as well as within the parenchyma of the lung. There was no associated necrosis. Kupffer cells of the liver were prominent and actively phagocytic, while periportal collections of large phagocytes were uniformly present. Lymphoid corpuscles of the spleen were inconspicuous, but innumerable large mononuclear cells, some occurring as nodular collections, were present in the sinusoids. Red-cell phagocytosis

Fig. 2 (Case 1).—Showing rash, adenopathy, and emaciation.

was marked in the spleen as well as lymph nodes and bone marrow. Small focal clumps of more immature mononuclear cells were present in the spleen. The lymph-node architecture was disrupted by infiltration of large phagocytic cells. Giant cells were also abundant, and only small groups of mature lymphocytic cells persisted. The same alterations were noted in the thymus, where the process was granulomatous in appearance. Normal bone-marrow elements were largely replaced with nodular formations of phagocytes, often with hemosiderin particles in their cytoplasm. Focal granulomas were present in the mucosa of the intestine and ureter and in the interstitial tissue of the pancreas. Similar collections were prominent in the cortex of the kidney, often in close proximity to a glomerulus but with no significant morphologic alteration of these structures or adjacent tubules. Focal tubular dilatations suggesting obstruction were noted.

Fig. 3 (Case 1).—Skin lesion, exhibiting nodular, subepidermal collection of large mononuclear cells. Note dessication and fragmentation of overlying epithelium.



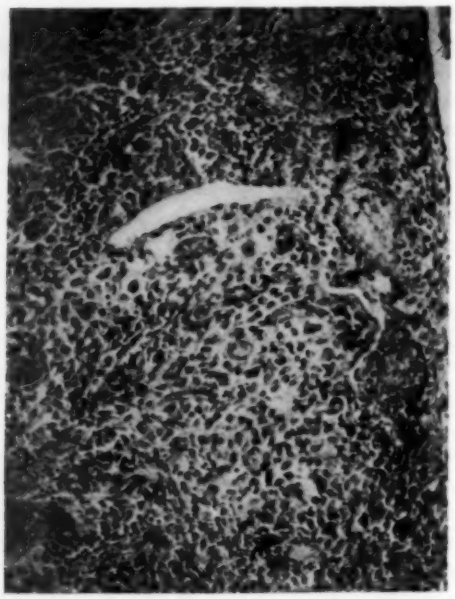


Fig. 4 (Case 1).—Lung. Nodular subpleural accumulation of huge mononuclear cells, lymphocytes, and some segmented cells.

Comment.—Pathologically this case exhibited all features necessary to establish the diagnosis of disseminated reticuloendotheliosis.

Case 2 (B. D.).—A one-year-old boy who was well until six months previously, when he developed purulent otorrhea and fever. This was followed by a rash appearing first on the forehead and hands and later covering the entire cutaneous surface. On hospital admission he was well nourished and developed, but pale and febrile with a generalized

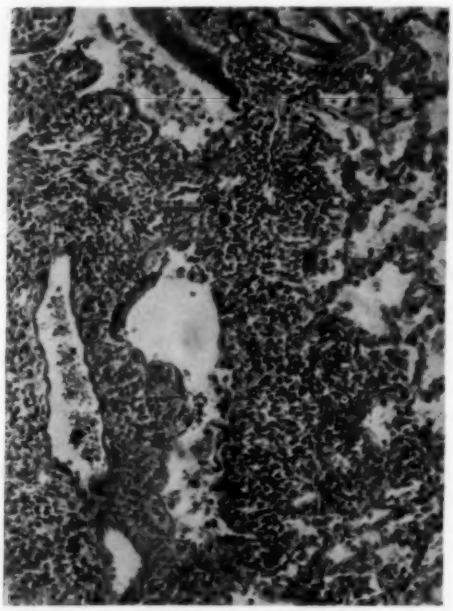


Fig. 5 (Case 2).—Lung, with distinctive infiltration of large histiocytes into interstitium about bronchi and vessels.

papular rash, particularly prominent over the scalp, neck, abdomen, and inguinal areas. Hepatosplenomegaly, otitis media, and lethargy were also present. Roentgenograms showed extensive pulmonary infiltration but normal bones. A simple mastoidectomy was performed because of persistent otorrhea. After one month's hospitalization, he developed pneumothorax and died shortly afterwards.

Autopsy.—The body was emaciated, though normally developed. There was a generalized papular skin rash, with hemorrhagic areas in many of the lesions. Shotty nodes were palpable in the cervical, axillary, and inguinal areas. The thymus seemed larger than normal, with one area of softening. The lungs were well expanded though slightly firm to palpation, while the liver was greatly enlarged, with fine nodularity on the surface and on cross section. Bile ducts contained inspissated bile, but the larger ducts were patent. The spleen was large, with a tense capsule, and cut surface showed no focal lesions. Both ureters exhibited diffuse mucosa thickening and granularity in their superior portions. The bone marrow was spongy and red.

Microscopic Examination.—The skin showed focal nodules of large histiocytic cells beneath the surface epithelium, often with associated hemorrhage. Sections of lymph nodes revealed a quantitative increase in large mononuclear cells within the sinusoids, though the over-all architecture was preserved. These cells exhibited marked phagocytosis of red cells and cellular debris and occasionally contained lipid droplets in their cytoplasm. The lungs showed a remarkable interstitial infiltration of the same large mononuclear cells, with a conspicuous localization of these cells in the peribronchial and perivascular areas (Fig. 5). In the liver the lobular pattern was accentuated by mononuclear cell accumulation, fibrosis, and bile-duct proliferation in the periportal areas. Intralobular bile stasis was evident, though the bile ducts contained no casts. In the spleen large mononuclear cells were conspicuous and formed nodular collections. Accumulations of large mononuclears and fibrous-tissue proliferation were also prominent in the sections of ureter, while focal collections of the same cells were evident in the mucosa of the stomach and gall bladder. A few small focal collections of large mononuclear cells were noted in the renal cortex. The thymus was very heavily infiltrated with these same cells; many had fat droplets in their cytoplasm. The bone marrow showed normal hemopoietic tissue, and large mononuclears were rare.

Comment.—Generally the lesions in different organs were similar, and eosinophiles were frequently present. A variable amount of fibrosis was evident in the hepatic, splenic, and uretheral lesions. Phagocytic activity of the characteristic cells was marked in some lesions and minimal in others. The pulmonary and hepatic lesions were particularly characteristic of acute disseminated reticuloendotheliosis.

Case 3 (G. F. C.).—A 3-month-old girl developed a rash on her legs three weeks prior to hospitalization and was eventually referred to Vanderbilt University Hospital because of extreme irritability, persistent fever, vomiting, and lethargy. She was well nourished and developed, but appeared extremely irritable, with a temperature of 102.6 F. Physical examination revealed a generalized maculopapular rash and secondary cutaneous infection with exfoliation. There was no evidence of adenopathy or hepatosplenomegaly. Bilateral pulmonary infiltration was present roentgenographically. She did poorly on symptomatic treatment, dying after several days. Reticuloendotheliosis was not suspected clinically.

Autopsy.—General development was normal, but subcutaneous edema was present. Encrusted pustular lesions covered the entire body, with areas of exfoliation. Neither external nor internal lymph nodes were appreciably enlarged. The serosal cavities showed no increased fluid. The lungs exhibited numerous areas of consolidation, more

evident posteriorly. The lymphoid tissue of the ileum was prominent, and the liver was not remarkable in size or appearance. The spleen was moderately enlarged, with firm consistency but without focal lesions. The remaining organs were within normal limits.

Microscopic.—Small amounts of coagulated protein were present in some alveoli. The most striking pulmonary change was a diffuse infiltration of histiocytes into the interstitial tissue, with thickening of alveolar septa and spillage of these cells into the alveolar spaces. Peribronchial and perivascular accumulations were prominent, but this process was somewhat patchy in distribution. Similar cells were present in small numbers in the interstitium of the heart, and heavy infiltrations of the same cells were seen in the thymus, the mucosa of the appendix, the ileum, and beneath the intact epithelium of the skin. The spleen showed numerous large hemosiderin-containing phagocytes in the sinusoids, the Malpighian bodies being small and inconspicuous. Lymph nodes showed the same infiltration of large phagocytic cells, with relative absence of lymphoid tissue. Focal accumulations of these large phagocytes were present about the portal triads of an otherwise normal liver. In the bone marrow the erythropoietic islands were scarce, but there was no significant infiltration of mononuclear cells. The renal cortex showed numerous focal accumulations of large mononuclear cells, often in proximity to normal glomeruli and tubules.

Comment.—No cultures were made at the time of autopsy. In this case there seemed to be a general atrophy of lymphoid tissue and a remarkable proliferation of large phagocytic cells. Lymph-node enlargement was not noted. The microscopic picture was that of disseminated reticuloendotheliosis.

Case 4 (M. J.).—A 9-month-old girl became ill four months prior to hospitalization. She rapidly developed generalized rash, bilateral otorrhea, increasing pallor, fever, irritability, and gingival bleeding. On physical examination she was poorly developed, undernourished, and critically ill. Generalized glandular enlargement, hepatosplenomegaly, anemia, and hemorrhagic maculopapular rash were present, the rash being more prominent about the scalp, shoulders, back, and inguinal areas. The clinical diagnosis was acute reticuloendotheliosis. Whole-blood transfusions and sulfathiazole were given, but after three days' hospitalization she was taken home, where she died. No tissues were examined microscopically; however, the clinical course and physical findings were classical of disseminated reticuloendotheliosis (Fig. 6).

Case 5 (E. D.).—This 7-month-old girl developed a pruritic maculopapular rash on her forehead several months prior to hospitalization. She did not respond to symptomatic treatment, and the lesions became more extensive, involving primarily the abdominal and inguinal regions in addition to the scalp. Two weeks prior to admission purulent nasal and oral discharge was noted. She was thought to have had intermittent low-grade fever for several weeks.

On hospitalization she was well nourished, well developed, restless, and irritable, with a seborrheic hemorrhagic rash on her scalp, trunk, and inguinal areas. She was pale and had otorrhea, stomatitis, gingivitis, hepatomegaly, and splenomegaly.

Blood culture showed no growth, but exudate from the auditory canal grew Staphylococcus aureus. Animals inoculated with blood and tissue of the patient remained healthy. Roentgenograms of bones were normal. Microscopically the skin lesions were typical of disseminated reticuloendotheliosis.

Fig. 6 (Case 4).—Dorsal view, showing characteristic rash.

Fig. 7 (Case 5).—Front view, showing characteristic rash.

She was given whole-blood transfusions but died after several weeks.

Biopsy of Skin.—The superficial epithelium was intact but thin over a 3 mm. area which represented the lesion. A mass of large mononuclear phagocytes with fairly abundant cytoplasm elevated the overlying epithelium and was sharply confined to the corium just beneath the surface epithelium. No appreciable phagocytosis was present, and, aside from extravasated red cells in the midportion, mononuclear cells made up the entire lesion.

Case 6 (W. B.).—This 6-month-old girl was well until two months prior to admission, when she developed anemia with loss of appetite and weight. Six weeks prior to admission she was given several whole-blood transfusions. At this time she had bilateral otorrhea and diminution of platelets. On hospitalization at Vanderbilt she was found to have anemia, edema, and hepatosplenomegaly in spite of the fact that she was well nourished and developed. No skin lesions or adenopathy were noted. She died three weeks later, with the clinical diagnosis of leukemia, although bone-marrow examination had not indicated such.

Autopsy.—The development and nutrition of the body appeared normal. The skin showed no lesions but was pale and yellow. The sclerae were not icteric. External lymph nodes were not palpable. The serosal cavities were free of fluid, while the heart and lungs were not remarkable grossly. Liver and spleen were markedly enlarged, but on cut section the liver contour and structure were normal except for a slight focal yellowish mottling. The spleen had a tense capsule and on cut section was soft and red with no focal lesions. There was a nodule of aberrant pancreatic tissue in the mesentery of the upper small intestine. No other gross abnormalities were noted.

Microscopic.—Focal interstitial accumulations of large mononuclear cells were seen in the lung, but such areas were not numerous. There was accentuation of the lobules of the liver due to collections of mononuclear phagocytes and round cells in the vicinity of the triads. Islands of hemopoietic tissue were present in the liver and in the spleen, both of which were congested and diffusely infiltrated by actively phagocytic histiocytic cells. The lymphoid nodules in the spleen were small and inconspicuous. A section of lymph node showed loss of germinal centers and infiltration with large mononuclear cells. Red-cell phagocytosis was very prominent in the lymph node and in the bone marrow. Hemopoietic tissue in the marrow seemed decreased in amount, and marrow spaces contained numerous large phagocytes. Aggregates of similar cells were prominent in the adrenal medulla, the

Fig. 8 (Case 6).—Kidney. Focal cortical infiltration of large mononuclears, lymphocytes, and some neutrophiles. Note normal glomeruli and dilated tubules.

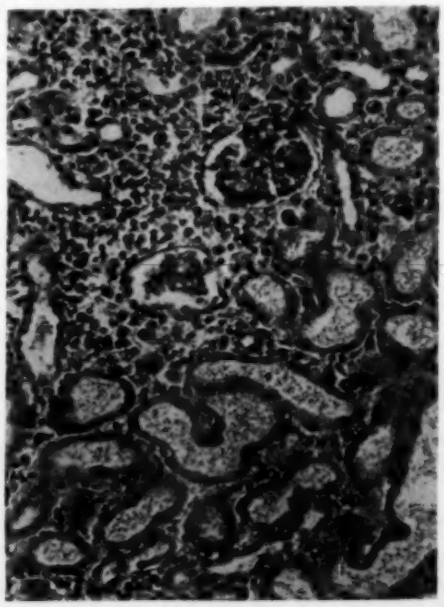


Fig. 9 (Case 7).—Photograph and roentgenogram showing rash, adenopathy, emaciation, and osteolytic lesions of skull.

interstitium of the pancreas, and focally throughout the renal cortex (Fig. 8).

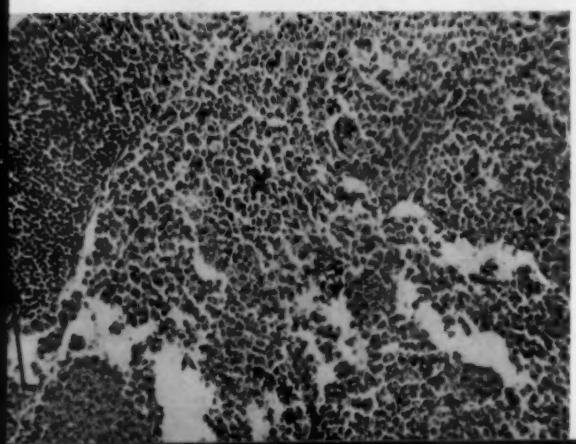
Proteus vulgaris was grown in a blood culture but was considered a contaminant.

Comment.—In this case, proliferation of actively phagocytic histiocytes was the most conspicuous feature. Atrophy of lymphoid tissue was prominent.

Case 7 (J. J.).—A 13-month-old boy three months prior to admission had a respiratory infection followed by persistent otorrhea and fever. A mass then developed in the posterior auricular region, and following mastoidectomy the operative wound continued to drain in spite of penicillin therapy. A few days before hospitalization, generalized maculopapular rash and petechiae appeared.

On physical examination the child was febrile, malnourished, irritable, and acutely ill. Both the primary and hemorrhagic rash were more pronounced in the skin folds, particularly the inguinal area. A destructive lesion was present behind the left ear, and hepatosplenomegaly was present. Roentgenograms revealed bilateral pulmonary infiltration and destructive areas throughout the skull, ribs, and extremities. The clinical diagnosis of disseminated reticuloendotheliosis was confirmed by lymph-node biopsy. He failed to respond to penicillin, 1200 r of x-radiation, and radioactive manganese. He died one month after being discharged from the hospital.

Fig. 10 (Case 7).—Lymph node with massive infiltration of histiocytic cells (*x*). Arrow indicates remaining lymphoid tissue.



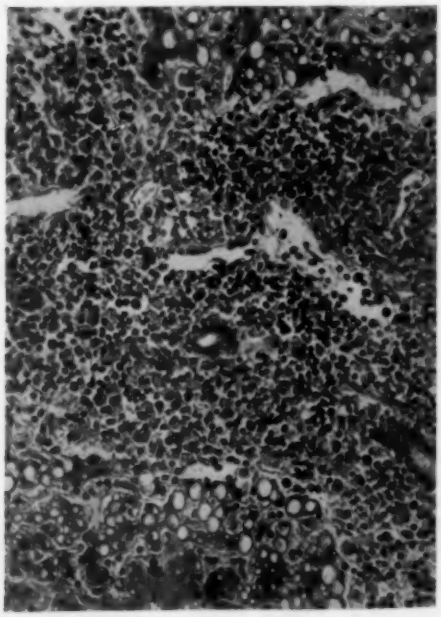
Biopsy of Lymph Node.—A few germinal centers persisted, but the lymphoid structure was largely replaced by massive infiltration of rather uniform cells of the histiocytic type (Fig. 10). The few remaining cords of lymphocytic cells were compressed. No necrosis was present. Isolated infiltrating cells

were quite like the phagocytic reticuloendothelial cells found in a normal lymph node. The nuclei were reniform or twisted, and the cytoplasm was fairly abundant, sometimes containing vacuoles and bits of phagocytosed debris. Occasional mitoses were encountered, and some eosinophiles were present. The impression was massive infiltration of lymph node by histiocytes of variable maturity with replacement of normal elements.

Case 8 (J. H. [Sibling of Case 15]).—A 14½-month-old boy five weeks prior to hospitalization developed rhinitis, bronchitis, fever, and increasing pallor. He was hospitalized because of diarrhea and abdominal enlargement. Physical examination revealed poor nutrition and development, marked irritability, fever, pallor, cervical adenopathy, hepatosplenomegaly, and anemia. He was thought to have histoplasmosis. Shortly after admission, hemorrhagic manifestations occurred. Treatment with penicillin, serum albumin, and whole-blood transfusions did not alter his course. He died two weeks after hospitalization.

Autopsy.—Nutrition and development of the body were normal. Petechiae were noted about the mouth. Firm, slightly enlarged lymph nodes were present in the cervical and inguinal regions, with masses of moderately enlarged, matted nodes in the mesenteric, periaortic, and hilar areas. Focal pulmonary atelectasis was present in the lungs. The liver was greatly enlarged but with a normal lobular pattern. The spleen was large, bloodly, and friable, with no focal lesions. The sternal bone marrow was dark red, while the vertebral marrow was pink and dry. An area of subarachnoid hemorrhage was present in the frontal area of the brain.

Fig. 11 (Case 8).—Liver, exhibiting periportal infiltrate.



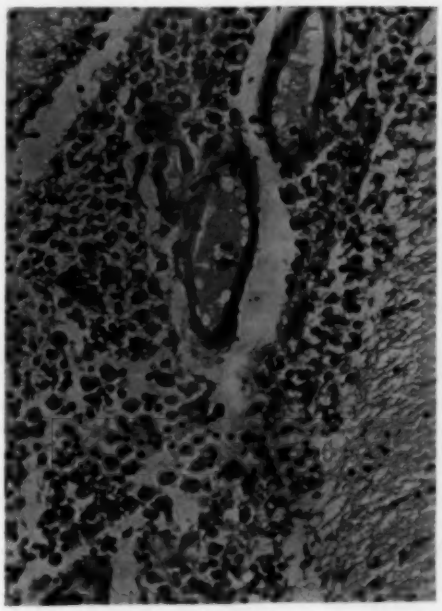


Fig. 12 (Case 8).—Cerebellum. Cellular infiltration into subarachnoid space.

Microscopic.—Peribronchial collections of large phagocytes were prominent in the lung, and nodular collections of similar cells with an admixture of lymphocytes were present in the duodenal mucosa. A granulomatous infiltration of large mononuclear cells, lymphocytes, and some eosinophiles was constantly present in the portal areas of the liver (Fig. 11). Similar infiltration was present in the interstitial tissue of the pancreas. The gall bladder wall, adrenal medulla, and prostate showed the same lesions, and nodular collections of histiocytes occurred focally in an otherwise normal renal cortex. The Malpighian bodies in the spleen were normal in appearance, but there was a diffuse and heavy infiltration of large mononuclear cells in the sinusoids, where red cell phagocytosis was marked. The architecture of the lymph nodes was maintained, but they contained tremendous numbers of large phagocytes. Many of these cells had vacuolated cytoplasm. The hemopoietic tissue of bone marrow was scanty, with large numbers of macrophages containing erythrocytes within their cytoplasm. Histiocytes and lymphocytes were present in the renal cortex.

Sections of the brain revealed marked infiltration of large phagocytic cells and round cells into the

meninges, and all sections of brain revealed perivascular cuffs of similar cells (Fig. 12).

Blood culture showed no growth, and attempts to isolate organisms from spleen, lymph nodes, and lungs were unsuccessful.

Comment.—This case exhibits the typical findings of disseminated reticuloendotheliosis. Cellular infiltration of the meninges was not seen in our other cases where the brain was examined.

CASE 9 (V. S.).—A 5-month-old girl was noted at birth to have small dark crusts over the palms, soles, trunk, and scalp. The lesions disappeared after one week, but during this time she developed cervical adenopathy and pain on movement. Three months prior to admission gingival bleeding was noted, and two months prior to admission a cystic mass developed in the right parietal area. She became very irritable and finally developed labored respirations. Roentgenograms revealed destructive changes throughout the pelvis and skull and pulmonary infiltration. The patient was referred to Vanderbilt University Hospital with the diagnosis of Letterer-Siwe's disease.

On physical examination she was critically ill, underdeveloped, and malnourished. She had palpable bony defects in the skull, pallor, generalized glandular enlargement, and hepatosplenomegaly. There was roentgenographic evidence of osteolytic lesions in extremities, skull, and pelvis; bilateral pulmonary infiltration, and right pneumothorax. Lymph-node biopsy confirmed the diagnosis of disseminated reticuloendotheliosis. She died approximately two months later.

Biopsy of Lymph Node.—The material from this case is no longer available for review. One of us orginally interpreted the microscopic changes as being typical of acute disseminated reticuloendotheliosis.

CASE 10 (B. D.).—A 4-week-old girl was hospitalized because of abdominal enlargement that had been noted for one week. Physical examination revealed the child to be poorly nourished and poorly developed, with hepatosplenomegaly, fever, and anemia. No rash was present, and x-rays of chest and bones were normal. Fever persisted on treatment with whole-blood transfusions, chloramphenicol (Chloromycetin), and chlortetracycline (Aureomycin). She developed bilateral otorrhea and died two weeks after hospitalization. The clinical diagnosis was acute disseminated reticuloendotheliosis.

Autopsy.—The body was emaciated, though fairly well developed. A few papules were present over the lower chest and abdomen and about the external genitalia. The superficial lymph nodes were not enlarged, and the mesenteric and hilar nodes were small and pink. Fibrinous adhesions were present at the right lung base. The lungs were well expanded and somewhat rubbery to palpation and showed some loss of crepitation. Two very small areas of suppuration were found at the right lung base. The liver was markedly enlarged, with millet-sized, yellow nodules beneath the capsule and on cut section. The spleen was very firm, with a few fibrinous adhesions over the surface, and cut section was dark maroon, firm, and friable. No other gross abnormalities were noted.

Microscopic.—Sections of skin revealed a diffuse scattering of mononuclear phagocytes in the corium. Similar cells were noted in the interstitium of the heart. Fibrin was present over the pleura, and the lungs showed a striking degree of infiltration with large phagocytic cells most prominent in the interstitial tissue. In many areas this was so massive as to obliterate the air sacs. In other areas the process was less marked. Periportal collections of similar large mononuclear cells were regularly present in liver sections. The spleen showed small lymphoid follicles, with nodular collections of rather immature mononuclear cells scattered through the engorged pulp. Numerous different lymph nodes showed the same picture of apparent loss of architecture, with only scattered lymphocytic clumps present. The sinusoids were filled with large mononuclear cells of varying maturity, but without nodule formation. No necrosis was present. The bone marrow showed normal elements, but histiocytes with phagocytosed red cells were numerous. Focal collections of similar large mononuclear cells were seen in the adrenal medulla and throughout the renal cortices.

Staphylococcus albus was grown from the lung but was thought to be a contaminant. Blood culture showed no growth.

Comment.—The microscopic lesions in the lymph nodes, spleen, liver, and lungs establish the diagnosis of acute disseminated reticuloendotheliosis.

CASE 11 (B. H.).—This 8-month-old girl three months prior to her first hospitalization developed cough, anorexia, and weight loss, followed one month later by "pneumonia" and ulceration of nasal and oral mucosa.

On physical examination, in addition to the ulcerative lesions, she had bilateral bronchopneumonia, pallor, and hepatosplenomegaly. She was thought to have histoplasmosis, but this could not be confirmed. She was dismissed from the hospital, but after fever recurred she was readmitted. There were many bleeding lesions on the mucocutaneous junction of the nose and mouth. X-rays revealed extensive pulmonary infiltration. Biopsy of the liver

confirmed the diagnosis of acute reticuloendotheliosis. She failed to respond to 900 r of x-radiation, was discharged from the hospital, and died shortly afterward.

Liver Biopsy.—The portal areas were accentuated by fibrosis and increased cellularity. Fibrous tissue and cellular infiltrate consisting of both macrophages and lymphocytes outlined the periphery of the liver lobule.

CASE 12 (W. W.).—This white boy was hospitalized at 6 months of age with lethargy from birth and intermittent diarrhea, vomiting, and fever developing more recently. The child was poorly nourished and could not roll over or support his head. A macular rash was present over the anterior chest, and hepatosplenomegaly was striking. Acute disseminated reticuloendotheliosis was suspected clinically and confirmed pathologically after splenectomy and lymph-node biopsy. Following x-radiation of the anterior and posterior abdomen, he was discharged improved but was readmitted at 8 months of age with bacteriologically proved pneumococcal meningitis. With this infection he had little febrile or leucocytic response. He appeared well after antibiotic therapy but was again admitted at ages 10 months, 13 months, and 16 months with pneumococcal meningitis. Attempts including craniotomy to determine a source of these infections were unsuccessful. The serum electrophoretic pattern was normal. The influence of splenectomy in infants as discussed by King and Shumacker [54] may have played a role in the recurrent infections of this patient, but obviously this cannot be incriminated in the face of his underlying disease.

During treatment of recurrent bouts of meningitis, signs of his original disease became less conspicuous, as evidence of central-nervous-system damage became more apparent. At the age of 2½ years his weight was 33½ lb. and there was no evidence of reticuloendotheliosis. He appeared mentally retarded.

Biopsy of Spleen and Liver.—The general architecture of the spleen was maintained, and the Malpighian bodies were normal. There was generalized increase in cellularity, and there were nodular accumulations of mononuclear cells (Fig. 13). These collections resembled tubercles without caseation. Many of the cells within the nodules had vacuolated cytoplasm. Neither foreign bodies nor doubly refractile material were found.

Cellularity of the portal areas of the liver was increased, with aggregates of large mononuclear cells, eosinophiles, plasma cells, and lymphocytes. Occasional nodules of mononuclear cells similar to those found in the spleen were present. There was moderate fatty degeneration of the liver cells.

Comment.—The tendency of large mononuclear cells to occur in nodular accumulations was pronounced in this case. These aggregations resemble the lesions of Boeck's sarcoid, and this diagnosis cannot be excluded entirely on the basis of the microscopic findings. The tendency of the large mononuclear cells to occur in nodules has been noted in other cases by ourselves and other authors.

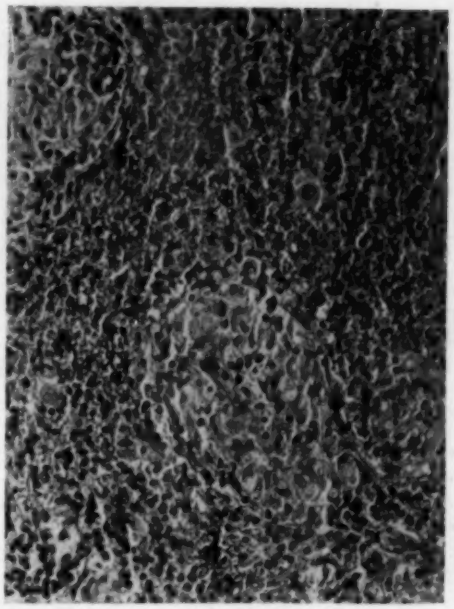


Fig. 13 (Case 12).—Spleen. Nodular accumulations of large mononuclear cells.

CASE 13 (M. H.).—This baby girl was noted to have a rash on her arms the first day of life. At 3 months of age she was thought to be allergic because of this and persistent diarrhea. At 5 months of age, after numerous formula changes, hepatomegaly was noted. At this time she also had anemia and mild generalized lymphadenopathy. Microscopic examination of skin and lymph node showed lesions typical of acute disseminated reticuloendotheliosis. Two lytic lesions of the skull were visible roentgenographically, but none were seen in the long bones. Since then and for 12 months she has received chlortetracycline. At the age of 17 months she weighs 25 lb. and is approaching a normal developmental level. The rash has disappeared, the liver and spleen are not enlarged, and the lytic skull lesions cannot be demonstrated.

Biopsy of Skin.—The architectural pattern was completely disrupted, with only a few lymphoid collections persisting beneath the capsule. These appeared compressed. The bulk of the node consisted of a syncytium-like accumulation of atypical mononuclear cells. These cells had distorted hyper-

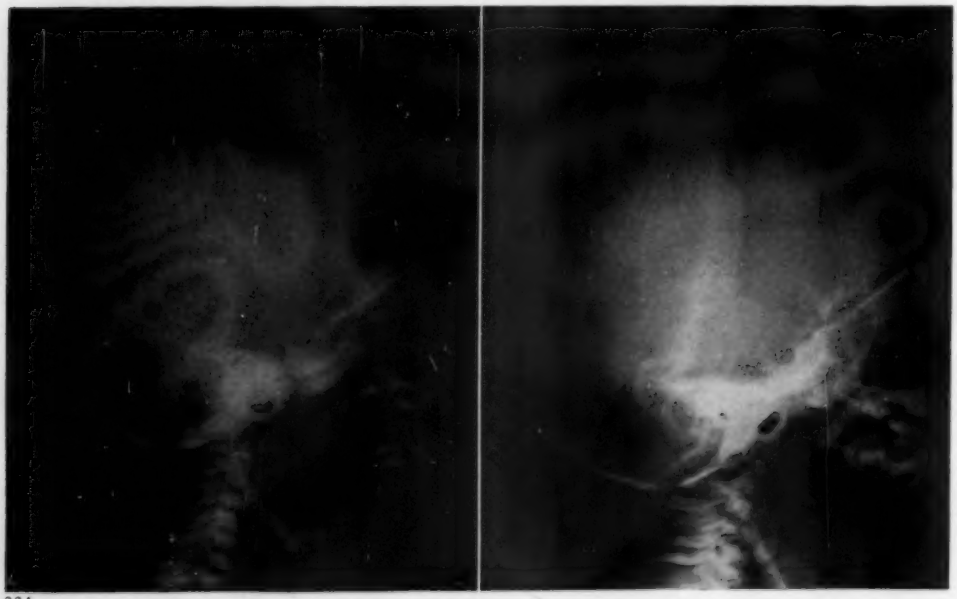
Fig. 14 (Case 13).—Before and after recovery.

chromatic nuclei. The cytoplasm of individuel cells was scanty and pink, with some phagocytosis. A few similar multinucleated giant cells were encountered. Eosinophiles were scattered about, though not in great numbers. No areas of necrosis were encountered.

Comment.—Skin and lymph-node lesions in this case were entirely characteristic of disseminated reticuloendotheliosis.

Case 14 (L. O.).—A 13-month-old girl four months prior to her first Vanderbilt hospitalization developed respiratory infection, with a mass in the left temporal area. This was followed by weight loss and massive nontender adenopathy in the neck, inguinal region, and both axillae. Inguinal lymph node biopsy was said to be compatible with some type of "xanthomatosis." Roentgenograms revealed bilateral pulmonary infiltration and multiple osteolytic areas in the skull, humerus, pelvis, and femur. Biopsy of these bone lesions was compatible with disseminated reticuloendotheliosis. She was discharged from the hospital doing poorly and finally developed marked periorbital edema, nausea, vomiting, and pallor. She was readmitted for whole-blood transfusions and x-radiation of her bone lesions. After discharge on chlortetracycline therapy, hospitalization was again necessary. She did

Fig. 15 (Case 13).—Roentgenograms before and after healing of osteolytic lesion.



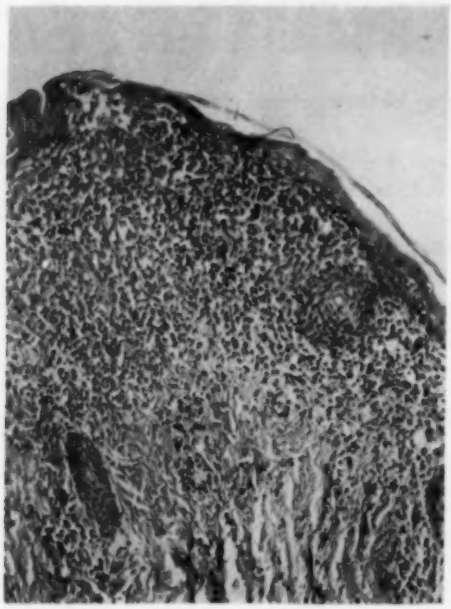


Fig. 16 (Case 13).—Skin, exhibiting focal mononuclear infiltration.

poorly and developed severe epistaxis, weight loss, generalized hemorrhagic rash, massive glandular enlargement, hepatosplenomegaly, ulcerative rhinitis, bilateral bronchopneumonia, and progression of the osteolytic areas throughout the skeleton. After developing bradycardia and labored respirations, she died with the clinical diagnosis of disseminated reticuloendotheliosis.

Biopsy of Lymph Nodes.—The pericapsular fat was infiltrated by lymphocytes. The germinal centers of the node were still evident in spite of massive infiltration of large pink-staining mononuclear cells (Fig. 18). Multinucleated giant cells were frequent, and clumps of polymorphonuclear leucocytes were evident. The picture was pleomorphic. In some places early fibrous tissue proliferation was evident, and necrosis had occurred in small areas. Some of the large phagocytes had foamy cytoplasm.

Subsequent lymph-node biopsies presented the same general changes described above. Eosinophiles were scattered throughout the lesions.

Biopsy of Skull.—A few spicules of bone were present, with the spaces containing rather dense fibrous connective tissue.

Autopsy.—The body was cachectic, and the skin was extremely pale, with a few petechiae over the extremities. All superficial lymph nodes were markedly enlarged, as were those of the mesentery and mediastinum. These nodes were firm and matted and on cut section were yellow, with occasional small areas of necrosis. The serosal cavities were normal. The lungs were well expanded but exhibited focal subpleural yellow infiltrations. The liver was markedly enlarged, with normal contours. The cut surface showed numerous yellow miliary lesions throughout, more prominent in the right lobe. The spleen was considerably enlarged and firm and on cut section showed many 1-2 mm. yellow foci. Innumerable translucent areas were present in the ribs, and section of these lesions revealed dry yellow lesions. Old blood was noted in the intestine, but no gastrointestinal lesions were demonstrable.

Microscopic Findings.—The lungs showed small cystic areas surrounded by massive accumulations of atypical histiocytic cells. There was no associated necrosis or leucocytic infiltration. In other areas the infiltration was less marked and confined

Fig. 17 (Case 14).—Photograph and roentgenogram, showing adenopathy and skull lesions.

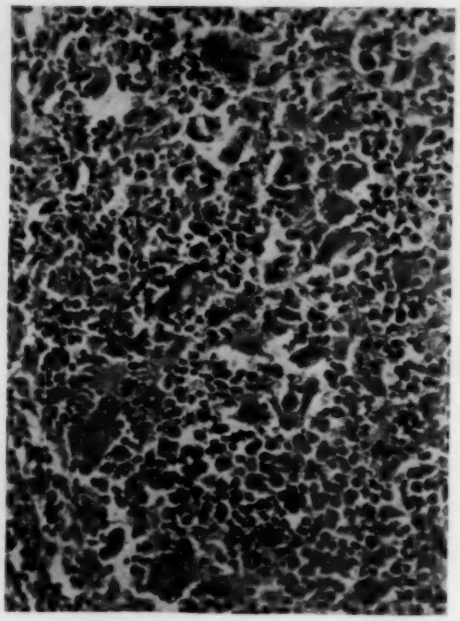


Fig. 18 (Case 14).—Lymph node. Giant cells, large mononuclears, polymorphonuclear leucocytes, and pyknotic fragments representing necrotic cells.

to alveolar septa. Many of these cells were vacuolated, and giant cells were occasionally encountered. In the liver there was marked periportal scarring, with bile duct proliferation. Only a few monocytes were seen in these lesions. There was no apparent bile retention, but Kupffer cells containing large amounts of hemosiderin were prominent. The spleen exhibited focal fibrotic areas, with much hemosiderin but no calcification. These lesions were scattered about, and lymphoid corpuscles were not found. Nodular accumulations of large mononuclear cells were found infrequently. The lymph nodes varied considerably in appearance. One was converted into a mass of fibrous connective tissue, while others showed no fibrosis. Several nodes had loss of usual architecture, with marked infiltration of atypical monocytes in addition to giant cells and small foci of polymorphonuclear cells. Hemosiderin was abundant in the large mononuclear cells. Infiltration of the pancreas and adrenal medulla by mononuclear cells was noted, while the kidney was free of focal infiltrations and other lesions. There was marked fibrosis in the marrow where small islands of erythropoietic tissue persisted. Scattered foci of large mononuclear cells were also present.

Blood culture showed no growth.

Comment.—The tissue changes in this case were in general the same as those seen in our other cases. Fibrosis, necrosis, and leucocytic infiltration were prominent. This case exhibits the variable histologic picture which may be present from time to time in the same or different organs. Diffuse cirrhosis of the liver was present. Dr. Charles Randall carried out tissue culture on spleen and lymph node in this case. The cellular growth was in the form of sheets of tumor-like cells. No evidence of an infectious agent was detected.

Case 15 (S. H. [Sibling of Case 8]).—The 3½-month-old white boy developed fever and irritability 10 days prior to admission. This was associated with abdominal distention and diarrhea. On admission to the hospital, he was found to be extremely pale, with slight adenopathy, hepatosplenomegaly, anemia, and dehydration. Liver and lymph-node biopsies were compatible with acute reticuloendotheliosis. He was unimproved after several whole-blood transfusions and was discharged to home care, dying approximately four months later.

Biopsy of Liver.—The lobular architecture was not distorted, and liver cells appeared normal. In the portal areas there were accumulations of large mononuclear cells with a few lymphocytes. This infiltration was definite though not marked.

Biopsy of Nodes.—The essential structure of the node was maintained, but the sinusoids could not be recognized due to massive infiltration of large mononuclear cells. These had pleomorphic nuclei, with a moderate amount of pink cytoplasm. These cells were not actively phagocytic and appeared to be immature histiocytes. There was no necrosis, and the picture was fairly uniform throughout the node. The capsule was intact.

CLINICAL COMMENT

A summary of the pertinent clinical and laboratory features of our cases is contained in Tables 1 and 2; however, certain observations deserve further comment.

There was an apparent direct relationship between the age of onset and the total duration of the illness, the younger patients surviving for only a few weeks, the older infants for months (Chart). Also, clinical manifestations of the disease were different in the various age groups. Young infants usually acquired secondary infections which in many instances occurred early enough to obscure the primary disease. Several were under medical care for such infections weeks prior

TABLE 1.—*Summary of Case Reports* *

Case	Sex	Race	Age Onset, Mo.	Duration, Mo.	Infiltrative Rash	Purpura or Petechiae	Bone Lesions	Pulmonary Infiltration (Roentgenographic)	Adenopathy	Liver Below C.M., Cm.	Spleen Below C.M., Cm.	Average Temp.	RBC, Millions	Hgb., Gm./100 Cc.	WBC, Thousands/Cu. Mm.	Otitis Media	Autopsy Pathological	Biopsy Confirmation	Present Status
1	M	W	10	6	X	X	X	X	X	6	4	102	2.3	8.0	4.6	0	X	:	Dead
2	M	W	7	7	X	0	X	X	X	6	2	101	3.9	10.3	19.0	X	X	:	Dead
3	F	W	3	1	X	0	0	X	0	0	0	103	3.2	10.5	12.5	0	X	:	Dead
4	F	W	5	4	X	X	Unkn.	Unkn.	X	6	6	102	1.9	4.5	12.6	X	:	:	Dead
5	F	W	3	4.5	X	X	0	Unkn.	X	4	8	102	4.2	11.0	20.0	X	X	X	Dead
6	F	W	3.5	2.5	0	X	Unkn.	X	X	6	6	103	1.0	3.6	7.3	X	X	:	Dead
7	M	W	10	8	X	0	X	Unkn.	X	4	2	101	3.2	9.0	8.1	X	:	X	Dead
8	M	W	13	2	0	X	Unkn.	Unkn.	X	4	4	102	4.6	11.5	29.0	0	:	X	Dead
9	F	W	3	5	X	X	X	X	0	5	4	100	2.6	7.5	28.5	0	:	X	Dead
10	F	W	1	1	X	X	Unkn.	Unkn.	0	2	2	101	3.6	6.6	2.0	X	X	:	Dead
11	F	W	5	5	0	0	0	X	X	6	6	102	5.5	11.0	15.6	0	:	X	Dead
12	M	W	5	36+	X	0	Unkn.	X	0	6	12	101	3.9	9.2	5.7	X	:	X	Living
13	F	W	3	14+	X	0	X	X	X	2	1	101	5.?	8.0	32.1	X	:	X	Living
14	F	W	9	12	0	X	X	X	X	6	4	102	0.9	3.0	0.5	0	X	:	Dead
15	M	W	8	4	0	0	0	X	0	8	4	101	3.4	7.5	5.4	0	:	X	Dead

* X indicates present; 0, absent.

TABLE 2.—*Summary of Fifteen Cases*

Fever (3 wk. to 8 mo.)	15
Anemia	15
Palpable liver and spleen	14
Maculopapular rash	10
Bronchopneumonia	10
Adenopathy	10
Otitis media	8
Hemorrhagic skin lesions	8
Bone lesions	5

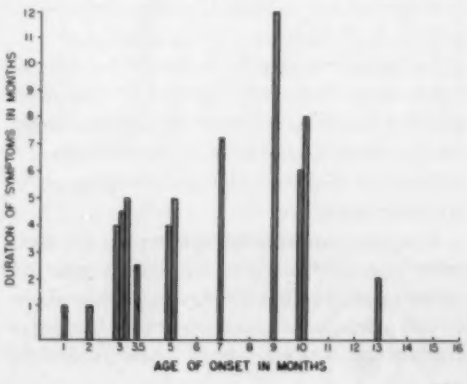
Race—15 white
Sex—6 males, 9 females

to the appearance of clinical signs and symptoms suggesting acute disseminated reticuloendotheliosis. Purulent otorrhea was present in over half of all patients, and two had mastoiditis. Other instances of secondary infections included pharyngitis, purulent rhinitis, gastroenteritis, impetigo, dissecting abscess of scalp, meningitis, pneumonia, and thrush. Bacterial and viral cultures revealed no common etiologic agent, and gamma globulin determination by paper electrophoresis was normal in the patient who had three recurrences of pneumococcic meningitis.

The significance of secondary infections and the possible alteration of immunologic response is not clear. Similar observations have been reported previously but probably without sufficient emphasis. It is interesting that many of the older infants had no evidence of secondary infections.

Pulmonary infiltration, present roentgenographically in several instances, was present pathologically in all patients so examined and consisted of unique interstitial pneumonitis

AGE OF ONSET COMPARED WITH DURATION IN FATAL CASES



with infiltration of large mononuclear cells. Secondary bronchopneumonia was not a common pathological finding.

Contrary to expectations, the characteristic maculopapular rash was not confined to the younger infants, and those who had no evidence of cutaneous infiltration were 3.5, 13, 5, 9, and 3 months of age. The rash usually appeared first in the scalp and hairline, later becoming generalized but always more pronounced in skin folds, such as the inguinal and axillary areas. Individual lesions were elevated, with a greasy-appearing, scaly surface. In several instances, the infiltrative rash seemed to herald the onset of the disease, and in one instance lesions were noted at birth. It should be emphasized that features of the rash were characteristic enough that many of our patients were diagnosed by its appearance alone.

The appearance and progression of hemorrhagic lesions seemed independent of the primary maculopapular rash. However, when the infiltrative rash was present hemorrhage was more pronounced within the individual lesions. Of the five patients who had no infiltrative skin lesions, three eventually had purpura or petechiae due to platelet deficiency, whereas five patients with diffuse generalized maculopapular rash showed no clinical evidence of cutaneous bleeding, although several had diminished platelets with prolonged bleeding time.

Generalized adenopathy was present in 10 patients, the extent being directly related to age. Older infants with a longer course developed marked adenopathy, while the five patients with no clinical adenopathy were only 1, 2, 3 (2 cases), and 5 months of age.

Hepatosplenomegaly, present in 14 patients, was also more marked in the older patients, but in no instance was the enlargement considered massive. Pathologically the increase in size seemed due entirely to cellular infiltration.

Bone lesions, present in five patients, were more common in older infants. It was impressive that under roentgenographic observation many lesions were obviously healing or completely healed, while new osteolytic lesions were appearing or becoming more extensive. Similar observations were made pathologically in that proliferative and healed lesions, osseous and visceral, could be observed simultaneously in the same patient.

We have attributed all hematologic manifestations to reticuloendothelial proliferation or hypoplasia of the bone marrow. This resulted in almost consistent lowering of platelets and hemoglobin.

While the total serum protein values were usually low, there was no consistency. In at least two cases, the globulin fraction was below 1 gm. per 100 cc. In Case 12, the serum electrophoretic pattern was normal.

It is interesting that several of our original cases, though clinically characteristic, were not diagnosed correctly prior to autopsy. Further experience with the disease enabled us to make the correct clinical diagnosis in 11 of the 15 cases. On occasion the rash may mistakenly be interpreted as an expression of eczema, seborrhea, exfoliative dermatitis, or even meningococcemia; whereas hepatosplenomegaly often leads one to consideration of leukemia, miliary tuberculosis, Banti's disease, Cooley's anemia, syphilis, or histoplasmosis.

We have been particulary concerned that acute disseminated reticuloendotheliosis not be confused with disseminated histoplasmosis, another rather common and usually fatal illness in our locality. The two entities have several similarities (Table 3), and this is not surprising, since both diseases, either primarily or secondarily, are associated with reticuloendothelial proliferation. Clinically, the two without the presence of rash or bone lesions may be indistinguishable, and unless

TABLE 3.—*Disease Similarities*

Features	Histoplasmosis	Disseminated Reticuloendotheliosis
Lymphadenopathy	++	++
Splenomegaly	++++	++
Hepatomegaly	++	++
Hemorrhage	++++	++++
Reticuloendothelial proliferation	++++	++++
Anemia	++++	++++
Rash	.....	+++
Bone lesions	.....	++

organisms are found pathological differentiation can be difficult. Histoplasma capsulatum has been easily cultured from all cases diagnosed pathologically as histoplasmosis, while such organisms have not been cultured from any diagnosed as acute disseminated reticuloendotheliosis, though special effort has been made to find and culture H. capsulatum. We have been impressed by the marked splenic enlargement usually present in histoplasmosis in contrast to slight enlargement seen in acute disseminated reticuloendotheliosis.

Two of our patients, Case 12 and Case 13, with biopsy-confirmed diagnoses are apparently cured. Both infants were quite young, 6 and 3 months of age, both had a maculopapular infiltrative rash, anemia, hepatosplenomegaly, and platelet diminution, and one patient had bone lesions. They appeared identical to those patients who had a fulminating clinical course, subsequently dying. It is possible that these cures were due to antibiotic therapy, but also conceivable that they represent extremely rare instances of spontaneous cure. It does not appear likely that splenectomy in one patient influenced the course of the disease.

Efforts to find an etiologic agent have been hampered by the unusual susceptibility of these patients to secondary infections, the signs of which may appear prior to recognizable symptoms of reticuloendotheliosis. All patients had fever which occurred early in the course of the illness. Our attempts to isolate a virus by tissue culture and chick-embryo techniques have failed on several occasions. For the above reasons we have no evidence for incrimination of any microorganism as an etiological agent, even though many bacteria have been cultured from tissues of our patients. It is interesting that two patients were siblings, although they were never in contact. The sibling of another patient died several years earlier with "leukemia associated with a rash." No biopsy or autopsy had been done on the first child, but the mother thought their symptoms identical.

We have no definite opinions as to the etiology of the disease. The possibilities of its being an infection, a tumor, a tissue reaction to viral or even bacterial agents, or an abnormal immunologic response still exists.

PATHOLOGY COMMENT

The cases which we have presented exhibit unique and constant lesions which justify their inclusion in one group designated acute disseminated reticuloendotheliosis. It is well to emphasize that final confirmation of this diagnosis rests on the demonstration of characteristic microscopic lesions, even though the gross autopsy findings usually suggest the basic disease. Thus the liver and spleen are enlarged, but the lesions accounting for the hepatosplenomegaly may vary from grossly visible nodules to those evident only on microscopic examination, though their essential character is the same. Areas of bone rarefaction and the skin rash are noteworthy gross findings; however, frequently secondary infection and hemorrhage alter the characteristic skin lesions greatly.

Focal aggregations of pleomorphic large mononuclear cells constitute the unit lesions of disseminated reticuloendotheliosis, but there is almost always an admixture of plasma cells and lymphocytes. Frequently eosinophiles and neutrophiles are present in appreciable numbers. The numbers and types of these adventitious cells determine the appearance of individual lesions and these factors account for the pleomorphic character of the lesions of disseminated reticuloendotheliosis, both in the same and in different cases. However, generalized proliferation of the large mononuclear cells apparently derived from the reticuloendothelial system must be present in order to establish the diagnosis.

Excellent descriptions of the pathology of disseminated reticuloendotheliosis are available in the papers of Abt and Denenholz,[16] Foot and Olcott,[40] Wallgren,[20] Mallory,[26] and Schafer.[32] Our findings have been consistent with those recorded by these authors. We will not dwell upon the detailed description of individual lesions or involvement of particular organs except as they pertain to certain features of the pathology which we will emphasize. We agree with the conclusion of other authors that the large mononuclears

seen in disseminated reticuloendotheliosis may in one instance resemble the normal large phagocytic cells and in another may appear neoplastic. Thus, in a single lymph node (Fig. 10) there is proliferation of immature mononuclear cells and obliteration of normal architecture to the extent that the diagnosis of reticulum-cell sarcoma is suggested, while in other areas of this same node the abundant large mononuclear cells are mature in appearance and phagocytosed debris is seen in their cytoplasm. Phagocytic activity of the large mononuclears is often prominent in this disease, and lipid droplets, hemosiderin, and pyknotic fragments may frequently be demonstrated within the cytoplasm of these cells. There is a tendency for these large mononuclear cells to replace the normal lymphoid structures, though as indicated previously the abnormal cellular deposits are not limited to these areas.

Nodular or diffuse infiltrations of large mononuclear cells may occur in unusual locations. For example, one case had infiltration of the subarachnoid space (Fig. 12). Infiltration of the pancreas, ureter, gall bladder, adrenal, and submucosa of the gastrointestinal tract in various sites occurred in different cases. Such lesions suggest tumorous deposits similar to those occasionally seen in leukemia.

The efforts to determine the etiology of disseminated reticuloendotheliosis on the basis of the microscopic findings have been unsuccessful. Our own case material illustrates the difficulties of exact interpretation of such a study. No organism is demonstrable in microscopic section, and the variability of the lesions has already been noted. Small foci of coagulative necrosis with collections of polymorphonuclear leucocytes may be seen in association with massive infiltration of immature large mononuclear cells. Fibrous-tissue proliferation may suggest the healing of an inflammatory process. In addition to necrosis, leucocytic infiltration, and fibrosis, large cells with lobate nuclei may resemble Reed-Sternberg cells closely and suggest Hodgkin's disease. Other authors have commented on this similarity.

Routine cultures, as well as fungus cultures and animal inoculation, have failed to yield information as to etiology in our autopsied cases. Tissue culture of spleen and lymph node from one case resulted in a sheet-like growth of neoplastic-appearing cells.

Certain microscopic lesions of acute disseminated reticuloendotheliosis merit further comment, since they are almost constant and of great value in establishing the anatomical diagnosis. Some of these lesions have been noted in previous reports, but our large number of cases affords a unique opportunity to study and compare a variety of cases. The diagnosis of acute disseminated reticuloendotheliosis is suggested by any one of the following lesions, while the occurrence of two or more makes the diagnosis almost certain.

The skin lesion, when fully developed, is distinctive (Figs. 3 and 16). Focal accumulations of atypical mononuclear cells confined to the corium and often in relation to a skin adnexal gland is peculiar to disseminated reticuloendotheliosis. This infiltration is usually accompanied by hemorrhage and dessication of overlying epithelium. These features account for the hemorrhagic character of the rash and the seborrheic appearance of individual lesions as seen clinically.

Lymphoid tissue, including lymph nodes, spleen, and thymus, are altered in a characteristic manner (Figs. 13 and 18). Atrophy of normal lymphoid elements is often conspicuous. For example, the Malpighian bodies of the spleen as well as the germinal centers of the lymph nodes may become atrophic and difficult to identify, especially with the constant proliferation of mononuclear cells further obscuring the normal anatomical features. The amount of cellular proliferation is extremely variable, and this explains the varying degrees of lymphadenopathy observed clinically. Because of this quantitative variability, the microscopic picture may be suggestive but not diagnostic when only a single superficial lymph node is available for study.

Bone-marrow changes may differ in degree but are generally characteristic. Atypical mononuclear cells may be present in large

numbers, but in several of our cases such infiltration was so minimal that the possibility of establishing the diagnosis by bone-marrow aspiration appeared unlikely. Atrophy of normal marrow constituents was present in several of our cases, and it seems that the anemia and low platelet counts with tendency to hemorrhage may result either from replacement by the large mononuclear cells or from this marked atrophy of erythropoietic tissue. Numerous phagocytic mononuclear cells containing quantities of cytoplasmic hemosiderin suggested abnormal hemolysis or a defect in pigment metabolism. Bone-marrow fibrosis was noted in an occasional case.

Infiltration into lungs, liver, and kidneys was so common and characteristic of acute disseminated reticuloendotheliosis that it may be considered almost specific for the disease. Interstitial infiltration of the pulmonary tissue was seen in every autopsied case. The submucosa of the bronchi and adventitia of vessels as well as the alveolar septa exhibited variable degrees of large mononuclear infiltration (Fig. 5). We have not seen this peculiar localization of large mononuclear cells in other disease states. Such infiltration may well obstruct the passage of air through the bronchi and across the alveolar membrane. In fact, cystic spaces seen in the lung parenchyma in one of our cases were interpreted as emphysematous blebs resulting from partial bronchiolar obstruction. Two patients were clinically diagnosed as having pneumothroax. In other instances, this pulmonary infiltrate may be nodular (Fig. 4), with the pleomorphism of the lesions seen elsewhere in the body. Eosinophiles, plasma cells, and lymphocytes as well as the characteristic large mononuclear cells are present in such nodules. Such infiltrations account for the diagnosis of "bronchopneumonia" oftentimes made clinically on the basis of x-ray examination.

Sections from the liver were available for study in 10 cases, and constant changes were noted, though these were not identical in every case. In each a unique infiltration of cells in the portal areas was present (Fig. 11). Plasma cells and lymphocytes were noted, in addition to the large mononuclear cells. In some cases this infiltration was massive enough to be grossly detectable, but in such instances the essential character of the lesions was the same as with those showing only microscopic changes. Variable degrees of fibrosis and bile-duct distortion were noted. Two cases with intralobular bile stasis showed fibrosis of sufficient degree to be classified as cirrhosis. Disseminated reticuloendotheliosis should be entertained as possible diagnosis in every case of infantile cirrhosis of the liver.

The final unique lesion of disseminated reticuloendotheliosis noted in our cases occurs in the kidney and was present in six of seven cases in which renal tissue was available for microscopic study. This consisted of focal cortical accumulations of large mononuclear cells, with some plasma cells and lymphocytes present. These lesions occurred in the periglomerular interstitial tissue, and there was no accompanying change in the glomeruli (Fig. 8). Dilatation of occasional tubules was associated with this infiltration and probably resulted from obstruction by the cellular masses. The localization and types of cells comprising the infiltrate make this lesion distinctive for disseminated reticuloendotheliosis.

SUMMARY AND CONCLUSIONS

The subject of acute disseminated reticuloendotheliosis of the nonlipid variety is reviewed, and 15 typical cases are reported. These infants, all 13 months of age or under, illustrate the classical clinical features of the disease, including maculopapular rash, hemorrhagic manifestations, anemia, generalized lymphadenopathy, moderate enlargement of the spleen and liver, susceptibility to secondary infection, and osteolytic lesions. These manifestations were all the result of reticuloendothelial proliferation and infiltration. The short duration of the disease in these patients probably accounts for the fact that lipid accumulation was minimal.

These data support the monistic concept originally proposed by Wallgren and later

extended by Farber. This concept suggests that Letterer-Siwe's disease, or acute disseminated reticuloendotheliosis, is but an infantile, usually fatal, form of a disease spectrum which in other age groups extends through Hand-Schüller-Christian's disease to eosinophilic granuloma. The manifestations are fortuitous, depending only on the age of the subject and the chance distribution of lesions, thus accounting for transitional forms. No etiological factor could be determined, but there is considerable pathological evidence to support infection as being of direct or indirect importance. Two biopsy-proved cases of acute disseminated reticuloendotheliosis are apparently well. Both patients received intensive antibiotic therapy.

REFERENCES

1. Letterer, E.: Aleukämische Retikulose (Ein Beitrag zu den proliferativen Erkrankungen des Retikuloendothelialapparates), Frankfurt Ztschr. Path. **30**:377, 1924.

2. Smith, T.: Skull-Cap Showing Congenital Deficiencies of Bone, Tr. Path. Soc. London **16**: 224, 1864-65.

3. Hand, A., Jr.: Polyuria and Tuberculosis, Arch. Pediat. **10**:673, 1893.

4. Kay, T. W.: Acquired Hydrocephalus with Atrophic Bone Changes, Exophthalmos and Polyuria, Pennsylvania M. J. **9**:520, 1905-1906.

5. Schüller, A.: Über eigenartige Schädeldefekte im Jugendalter, Fortschr. Geb. Röntgenstrahlen **23**:12, 1915.

6. Christian, H. A.: Defects in Membranous Bone, Exophthalmos and Diabetes Insipidus, in Contributions to Medical and Biological Research: Dedicated to Sir William Osler, Bart., M.D., F.R.S., in Honor of His Seventieth Birthday, July 12, 1919, by His Pupils and Co-Workers, New York, Paul B. Hoeber, Inc., 1919, Vol. 1, pp. 390-401.

7. Weidman, F. D., and Freeman, W.: Xanthoma Tuberosum: Two Necropsies Disclosing Lesions of Central Nervous System and Other Tissues, Arch. Dermat. & Syph. **9**:149, 1924.

8. Rowland, R. S.: Xanthomatosis and the Reticuloendothelial System: Correlation of an Unidentified Group of Cases Described as Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus (Christian's Syndrome), Arch. Int. Med. **42**:611, 1928.

9. Epstein, E.: Die generalisierten Affektionen des histiozytären Zellensystems, Med. Klin. **21**: 1501, 1925.

10. Chester, W.: Über Lipoidgranulomatose, Virchows Arch. path. Anat. **279**:561, 1930.

11. Henschen, F.: Über Christians Syndrom und dessen Beziehungen zur allgemeinen Xanthomatose, Acta pædiat. (Supp. 6) **12**:1, 1931.

12. Sosman, M. C.: Xanthomatosis (Schüller-Christian's Disease; Lipoid Histiocytosis), J. A. M. A. **98**:110, 1932.

13. Rowland, R. S.: II. Constitutional Disturbances of Lipid Metabolism, in Brenneman's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 3, Chap. 23, p. 15.

14. Fraser, J.: Skeletal Lipoid Granulomatosis (Hand-Schüller-Christian's Disease), Brit. J. Surg. **22**:800, 1935.

15. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of 22 Cases, Ann. Int. Med. **11**:1662, 1938.

16. Abt, A. F., and Denenholz, E. J.: Letterer-Siwe's Disease: Splenohepatomegaly Associated with Widespread Hyperplasia of Nonlipoid-Storing Macrophages; Discussion of the So-Called Reticulo-Endothelioses, Am. J. Dis. Child. **51**:499, 1936.

17. Goldzieher, M. A., and Hornick, O. S.: Reticulosis, Arch. Path. **12**:773, 1931.

18. Siwe, S. A.: Die Reticuloendotheliose—ein neues Krankheitsbild unter den Hepatosplenomegalien, Ztschr. Kinderh. **55**:212, 1933.

19. Galeotti Flori, A., and Parenti, G. C.: Reticuloendoteliosi iperplasica infettiva ad evoluzione granuloxantomatosa (tipo Hand-Schüller-Christian), Riv. clin. pediat. **35**:193, 1937.

20. Wallgren, A.: Systemic Reticuloendothelial Granuloma: Nonlipoid Reticuloendotheliosis and Schüller-Christian Disease, Am. J. Dis. Child. **60**:471, 1940.

21. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating Primary Neoplasm, Am. J. Path. **16**:479, 1940.

22. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone with Report of a Case, Am. J. Path. **16**:595, 1940.

23. Bass, M. H.: Solitary Eosinophilic Granuloma of Bone, Am. J. Dis. Child. **61**:1254, 1941.

24. Hatcher, C. H.: Eosinophilic Granuloma of Bone, Arch. Path. **30**:829, 1940.

25. Farber, S.: The Nature of "Solitary or Eosinophilic Granuloma" of Bone, abstracted, Am. J. Path. **17**:625, 1941.

26. Mallory, T. B.: Pathology: Diseases of Bone, New England J. Med. **227**:955, 1942.

27. Eosinophilic Granuloma of Bone, Correspondence, J. A. M. A. **135**:935, 1947.

28. Thannhauser, S. J.: Eosinophilic Granuloma of Bone, J. A. M. A. **134**:1437, 1947; Correction **135**:46, 1947.

29. Weinstein, A.; Francis, H. C., and Sprofkin, B. F.: Eosinophilic Granuloma of Bone: Report of a Case with Multiple Lesions of Bone and Pulmonary Infiltration, Arch. Int. Med. **79**:176, 1947.

30. Weaver, E. N., and Carter, J. R.: Eosinophilic Granuloma of Bone, U. S. Nav. M. Bull. **47**:1066, 1947.

31. Laymon, C. W., and Sevenants, J. J.: Systemic Reticuloendothelial Granuloma: Comparison of Letterer-Siwe Disease, Schueller-Christian Disease and Eosinophilic Granuloma, Arch. Dermat. & Syph. **57**:873, 1948.

32. Shafer, E. L.: Nonlipid Reticulo-Endotheliosis: Letterer-Siwe's Disease; A Report of 3 Cases, Am. J. Path. **25**:49, 1949.

33. Schuknecht, H. F., and Perlman, H. B.: Hand-Schüller-Christian Disease and Eosinophilic Granuloma of the Skull, Ann. Otol., Rhin., & Laryng. **57**:643, 1948.

34. Havard, E.; Rather, L. J., and Faber, H. K.: Non-Lipoid Reticuloendotheliosis (Letterer-Siwe's Disease), Pediatrics **5**:474, 1950.

35. Curtis, A. C., and Cawley, E. P.: Eosinophilic Granuloma of Bone with Cutaneous Manifestations: Report of Case, Arch. Dermat. & Syph. **55**:810, 1947.

36. Arnold, H. L.: Eosinophilic Granuloma of Bone: Preliminary Report of a Case Complicated by Lung Lesions, Proc. Staff Meet. Clin., Honolulu **12**:183, 1946.

37. Weidman, F. D.: The "Eosinophilic Granulomas" of the Skin. Arch. Dermat. & Syph. **55**: 155, 1947.

38. Freud, P.: Evolution of Systemic Reticuloendotheliosis in Childhood, J. Pediat. **38**:744, 1951.

39. Freund, M., and Ripps, M. L.: Hand-Schüller-Christian Disease: A Case in Which Lymphadenopathy Was a Prominent Facture, Am. J. Dis. Child. **61**:759, 1941.

40. Foot, N. C., and Olcott, C. T.: Report of Case of Non-Lipoid Histiocytosis (Reticuloendotheliosis) with Autopsy, Am. J. Path. **10**:81, 1934.

41. Siwe, S. A.: The Reticuloendothelioses in Children, in Levine, S. Z.; Butler, A. M.; Holt, L. E., Jr., and Weech, A., Editors: Advances in Pediatrics, New York, Interscience Publishers, Inc., 1949, Vol. 4, p. 117.

42. Dennis, J. W., and Rosahn, P. D.: The Primary Reticuloendothelial Granulomas with Report of an Atypical Case of Letterer-Siwe's Disease, Am. J. Path. **27**:627, 1951.

43. Fisher, R. H.: Multiple Lesions of Bone in Letterer-Siwe's Disease, J. Bone & Joint Surg. **35A**:445, 1953.

44. Nixon, J. W., and Perry, J. F., Jr.: Reticuloendothelial Hyperplasia of Bone: Report of Case of Letterer-Siwe's Disease, J. Internat. Coll. Surgeons **13**:788, 1950.

45. MacKelvie, A. A., and Park, W. W.: Letterer-Siwe's Disease, Arch. Dis. Child. **25**:955, 1942.

46. Steele, H. D.: Letterer-Siwe's Disease: Report of Case, Arch. Pediat. **67**:205, 1950.

47. Versiani, O.; Figueiro, J. M., and Junqueira, M. A.: Hand-Schüller-Christian's Syndrome and "Eosinophilic or Solitary Granuloma of Bone," Am. J. M. Sc. **207**:161, 1944.

48. Engelbreth-Holm, J.; Teilum, G., and Christiansen, E.: Eosinophilic Granuloma of Bone: Schüller-Christian's Disease, Acta med. scandinav. **118**:292, 1944.

49. Agress, H., and Gray, S. H.: Histoplasmosis and Reticuloendothelial Hyperplasia, Am. J. Dis. Child. **57**:573, 1939.

50. Carrington, G. L., and Davison, W. C.: Multiple Osteomyelitis Due to Bacillus Paratyphosus, Bull. Johns Hopkins Hosp. **36**:428, 1925.

51. Love, F. M., and Fashena, G. J.: Eosinophilic Granuloma of Bone and Hand-Schüller-Christian Disease, J. Pediat. **32**:46, 1948.

52. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. **24**:499, 1942.

53. Lackey, R. W.; Leaver, F. Y., and Farinacci, C. J.: Eosinophilic Granuloma of Lung, Radiology **59**:504, 1952.

54. King, H., and Schumacker, H. B., Jr.: Splenic Studies: I. Susceptibility to Infection After Splenectomy Performed in Infancy, Ann. Surg. **136**:239, 1952.

55. Christie, A.; Batson, R.; Shapiro, J. L.; Riley, H. D., Jr.; Laughmiller, R., and Stahlman, M.: Acute Disseminated (Non-Lipid) Reticuloendotheliosis, Acta pædiat. **43**:65, 1954.

56. Lichtenstein, L.: Histocytosis X: Integration of Eosinophilic Granuloma of Bone, "Letterer-Siwe Disease," and "Schüller-Christian Disease" as Related Manifestations of a Single Nosologic Entity, Arch. Path. **56**:84, 1953.

57. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: A Condition Affecting One, Several or Many Bones, but Apparently Limited to the Skeleton, and Representing the Mildest Clinical Expression of the Peculiar Inflammatory Histiocytosis also Underlying Letterer-Siwe Disease and Schüller-Christian Disease, Arch. Path. **37**:99, 1944.

VITAMIN B_6 DEFICIENCY IN INFANTS

A Follow-Up Study

DAVID BAIRD COURSIN, M.D., Lancaster, Pa.

IN JANUARY, 1954, a new syndrome of abnormal central nervous system activity in young infants was reported.* This consisted of increased irritability, gastrointestinal distress, aggravated startle response, and convulsive seizures. The symptoms were shown to respond to pyridoxine therapy with both clinical and electroencephalographic improvement. These observations confirmed earlier ones by Snyderman, Carretero, and Holt and established the importance of vitamin B_6 in infant nutrition.† It is significant to note that the conditions surrounding the appearance of these symptoms were such as to have produced borderline deficiencies of the vitamin rather than complete avitaminosis. This circumstance has provided a unique opportunity for evaluating the effects of suboptimal tissue levels of this substance during a particularly susceptible stage of human development. Furthermore, these findings have prompted an extensive evaluation of vitamin B_6 in milk preparations used in infant feedings. These two aspects of the problem will be considered in this paper.

METABOLIC CHANGES COINCIDENT WITH LOW VITAMIN B_6 INTAKE

The biochemical importance of vitamin B_6 has been recognized for some time.[5] Vitamin B_6 is known to have three main components: pyridoxine (the vitamin B_6 of pharmaceutical preparations) pyridoxamine, and pyridoxal. Of these three components, pyridoxine is stable to heat while the latter two are thermolabile. All of these forms are interchangeable through chemical reactions within the body. However, pyridoxal phosphate is the form that serves as a coenzyme in intracellular metabolism. Biochemically it enters into a number of reactions, the most important of which include transamination, deamination, decarboxylation, and desulfhydration.

The literature contains many excellent articles on the effects of complete vitamin B_6 deficiency in animals. These include acrodynia and alterations in growth,[5] production of red blood cells,‡ development of immune bodies,§ defects in amino acid metabolism,‖ and convulsive seizures.¶ In contrast to animal experimental diets, which are almost completely free of vitamin B_6, the feedings of the human infants studied contained about 60γ per liter. The milk formula was liquid S-M-A, which consists principally of defatted cow's milk, vegetable and animal fats, and vitamins, plus iron. This apparently complete formula probably accounted for the absence of obvious changes in growth, red cell formation, and apparent immunity. The level of vitamin B_6, however, did not prove adequate in fulfilling the body needs for central nervous system activity, amino acid metabolism, and electrolyte control. The absence of anemia and the higher sensitivity of the nervous system in partial vitamin B_6 deficiency in these infants may have been conditioned by their ages of 3 to 6 months.

Submitted for publication April 4, 1955.

From the Research Institute, St. Joseph's Hospital.

Supported in part by a grant (B-579) from the Neurological Institute, National Institutes of Health, United States Public Health Service.

* References 1 and 2.

† References 3 and 4.

‡ References 6 and 7.

§ References 8 and 9.

‖ References 10 and 11.

¶ References 12 and 13.

Clinically, these patients exhibited repeated seizures that were usually of short duration. These were variously described as staring spells, rigid opisthotonos, and generalized shaking with transient cyanosis. The symptoms were most noticeable on stimulation from movement, feeding, and sound. Electroencephalograms were done on 28 patients; abnormalities were noted during seizures. No characteristic pattern or interseizure residual was noted on any of the tracings. Of this group, six infants had simultaneous exposure to controlled auditory stimuli during their EEG recordings. All of these showed lowered thresholds of reaction and demonstrated clinical and electroencephalographic responses in excess of those seen in normal controls of the same age group.

These changes represented definite deviation from normal thresholds and supplied specific information on the alterations in central nervous system activity. The picture of lowered thresholds and increased excitability was shown to be readily corrected by the addition of 200γ per liter of pyridoxine hydrochloride to the diet. Clinical symptoms disappeared, and electroencephalograms remained normal.

Other metabolic changes have been determined by Hansen and his co-workers,[13] who have done amino acid and electrolyte studies in infants on the original diet low in vitamin B_6 followed by supplemental pyridoxine. They have shown that test doses of *l*-tryptophan given to these infants produce in their urine appreciable amounts of xanthurenic acid, which, in pyridoxine-deficient animals, is excreted after the ingestion of tryptophan. The addition of 0.5 mg. pyridoxine to the diet prevented this abnormal excretion.[14] A second experiment was performed to measure the effect of pyridoxine ingestion on the retention of magnesium, potassium, calcium, and phosphorus. During periods of deficiency, there was poor retention of these minerals. This state was corrected by treatment with 10 mg. pyridoxine daily.[15] These findings have provided further biochemical information that may contribute to a better understanding of some of the factors involved in the nervous system activity of these patients.

FOLLOW-UP STUDY OF CORRECTED VITAMIN B_6 DEFICIENCIES

The original group of 54 patients seen in our Pediatric Department demonstrated degrees of severity of their syndrome ranging from simple increased irritability to status epilepticus. The more severe cases were hospitalized, and complete studies including electroencephalograms were made. Of 28 patients who had had EEG studies, 20 were available for follow-up clinical and EEG evaluation at intervals of from six months to three years. Each of them had been fed on diets supplying an increased vitamin B_6 intake shortly after recognition of their problem.

Physical examination of these patients showed them to have followed normal growth and development patterns for their ages. Psychological and neurological testing did not reveal any abnormalities or evidence of mental retardation. None of these patients had experienced a recurrence of seizures since the initial episodes. This observation held true also for those children who had been subject to febrile illnesses during the interim. There was no obvious evidence of anemia or apparent increased susceptibility to infections that might have been the result of poor immune body response. Electroencephalographic tracings were repeated, with the routine finding of normal development of brain-wave patterns for age in comparison to those obtained earlier. There were no alterations in expected threshold responses to external and auditory stimuli.

Of the patients followed, one of the most interesting was an infant who had experienced an extreme reaction to the deficiency, with status epilepticus and cyanosis. He responded to 100 mg. of pyridoxine intramuscularly with improvement in EEG tracing within one mintue and clinical change to sound sleep within five minutes after injection. The baby was completely free of hyperactivity and convulsive seizures from then on, although he was maintained on his

original diet of 60γ per liter for the succeeding 84 days. He was then placed on a normal diet with adequate vitamin B_6 content and has continued to do well.

These findings have raised a number of questions with regard to individual susceptibility and response to different dosages of pyridoxine. It is of interest that of the many thousands of infants fed the diet low in vitamin B_6, the incidence of overt convulsive seizures was quite low. Sedation and formula changes may well have obscured the real scope of the numbers effected, but a national survey revealed only 300 cases with severe irritability. It would appear that some selective conditions must prevail in order to give rise to clinical symptoms. Perhaps these patients were born with a low level of vitamin B_6 and had this situation further aggravated by a poor dietary supply of the vitamin. Secondly, they may have had either an inherent need for higher levels of vitamin B_6 or may have had lower thresholds of reaction that were stimulated by intracellular metabolism in the absence of adequate vitamin B_6. One infant with an unusually high requirement of vitamin B_6 has been reported by Hunt and co-workers.[19]

Certain observations are worth considering in exploring this problem. We have found that seizures due to vitamin B_6 deficiency may be relieved by changing the infant's diet to simple lactose water. However, the addition of protein to the diet caused a reappearance of irritability and convulsions. By further formula change, it was possible to produce improvement again by increasing the dietary intake of vitamin B_6 by 200γ per liter. A return to the original formula caused seizures again within several days.

This observation is in agreement with work done by Boxer,# who showed that the addition of 1 or 5 mg. of pyridoxine hydrochloride to the routine diet of normal humans created a measurable increase in blood levels of the vitamin. This increase rapidly stabilized the blood content of vitamin B_6 at a new level, depending on the dosage received. Cessation of this supplement was followed by return to the original baseline values within a few days. This information substantiates the premise that certain daily requirements for the vitamin must be met in order to maintain a given blood level and normal nervous system activity. However, in the case described,[1] an excessive amount of pyridoxine altered some mechanism in such a fashion as to have permitted prolonged normal activity. This was far in excess of what might be explained on the basis of sustained blood levels or storage of vitamin B_6 and suggests some permanent changes in the enzyme system controlling energy transfer within the cell.

*Vitamin B_6 Content of Infant Feedings**

Milk or Milk Product	Per Cent Protein	Vitamin B_6 Content, γ/L. (Average)†	Per Cent of Original‡
Unprocessed			
Human milk	1.2	130	..
Cow's milk	3.25	580	..
Skim cow's milk	3.25	560	..
Sterilized liquids§			
Evaporated cow's milk	3.25	320	55
Infant Formula A	2.2	170	43
Infant Formula B	2.8	190	38
Infant Formula C	1.75	100	32
Infant Formula D	2.6	220	48
Infant Formula E	2.2	130	33
Infant Formula F‖	1.5	610	..
Spray-Dried Powders§			
Cow's milk	3.25	470	61
Skim cow's milk	3.25	520	60
Infant Formula A	2.2	310	79
Infant Formula C	1.75	260	83
Infant Formula G	2.0	240	67
Infant Formula F‖	1.5	610	..

* Based upon Table 1, in Hassinen, Durbin, and Bernhart.[16]

† Vitamin B_6 activity in comparison to the vitamin B_6 activity of pyridoxine hydrochloride. All values listed in this paper, as well as in the references cited, are 1.21 times larger than they would be had pyridoxine itself been used as the standard.

‡ The percentage loss was calculated on the assumption that the fresh milk used contained 580 γ/L. As commercial infant formulas vary in their content of milk solids, the level of vitamin B_6 supplied by milk in these was corrected by multiplying 580 by the fraction $\frac{\%\text{ milk protein in formula as fed}}{3.25\ (\%\text{ protein in cow's milk})}$

§ Values given are for reconstituted products.

‖ Fortified with pyridoxine hydrochloride.

VITAMIN B_6 IN INFANT FEEDINGS

The realization of the importance of vitamin B_6 in the infant diet has stimulated a

Boxer, G.: Personal communication to the author.

number of surveys of its presence in milk and milk substitutes. The Table lists the vitamin B_6 content of a number of the more widely used infant formulas.[16] The values presented were obtained through testing the reconstituted formulas by the Saccharomyces carlesbergensis method, which measures total activity for all forms of the vitamin.[17]

It is evident from this collection of data that infant feedings have a wide variety of vitamin B_6 contents. Human milk, with a lower concentration of vitamin B_6, appears to provide amounts adequate for metabolism. Hassinen and co-workers [16] found an average of 130γ per liter in human milk, with a range of 35γ to 220γ per liter. Whole cow's milk was found to have higher values, with an average of 580γ per liter, which is markedly altered by the process of sterilization to 280γ per liter. Commercial preparations have a broad range of vitamin B_6; the vitamin B_6 requirement of the infant may vary somewhat, depending upon the composition of the diet fed. However, Tomarelli and coworkers [18] found that the microbiological assay of heat-sterilized milk is not a true measure of the biological availability of the vitamin B_6. When rats were fed, the biological assay of heat-sterilized milk yielded vitamin B_6 values which were lower than those obtained by the microbiological method. With spray-dried milk, on the contrary, the bioassay and the microbiological method were in agreement. Routine processing of milk products causes definite decrease in their content of the pyridoxal and pyridoxamine components of the vitamin B_6 complex. This effect particularly occurs in autoclaving for sterilization, where temperatures in the neighborhood of 245 F may be used for 15 minutes or longer. The procedure initiates destruction of the pyridoxal and pyridoxamine content, which continues for a period of 10 days before reaching chemical equilibrium.[16] Depending on time and temperature factors, the final value may be reduced to as little as 30% of the original content.

Destruction of naturally occurring vitamin B_6 during autoclaving, a possible effect of the variety of nutrients (protein, fat, and carbohydrate), and a variation in the requirements of infants for vitamin B_6 were previously unrecognized phenomena. Since the concentrated liquid formula has been fortified with heat-stable pyridoxine hydrochloride (Table, Infant Formula F) no new cases of irritability have been reported in infants fed exclusively on this formula. A series of 300 infants have been followed in this and in many other departments, with no findings of deviation from normal growth and development or central nervous system hyperactivity.

It is evident from information at hand that the human infant has definite requirements for vitamin B_6 in a number of metabolic functions. The exact requirement varies with the individual patient but, in general, the diet must contain at least 100γ per liter in the presence of a dietary formulation which will permit maximum utilization of the vitamin. Alterations in milk chemistry and treatment with heat will require higher levels of vitamin B_6, ranging upward to 500γ per liter, in order to insure adequate amounts for body use.

SUMMARY

Vitamin B_6 is shown to be necessary in the diet of the human infant. A suboptimal dietary intake of 60γ per liter produce lowered thresholds of central nervous system activity, increased xanthurenic acid excretions, and lowered retention of the electrolytes—magnesium, potassium, calcium, and phosphorus.

Patients whose dietary deficiency of vitamin B_6 was promptly corrected showed immediate cessation of symptoms. Continued adequate daily intake prevented recurrences of symptoms and sequelae from the original episodes. No residual physical or electroencephalographic findings have been observed.

Milk preparations used in infant feeding have a wide variety of vitamin B_6 contents. The product levels are subject to changes by processing, especially from heat in autoclaving. The chemical constituents of the

milk formula may influence the degree of metabolic utilization of the vitamin within the body.

REFERENCES

1. Coursin, D. B.: Convulsive Seizures in Infants with Pyridoxine-Deficient Diet, J. A. M. A. **154**:406-408, 1954.

2. Molony, C. J., and Parmelee, A. H.: Convulsions in Young Infants as a Result of Pyridoxine (Vitamin B_6) Deficiency, J. A. M. A. **154**:405-406, 1954.

3. Snyderman, S. E.; Carretero, R., and Holt, L. E., Jr.: Pyridoxine Deficiency in the Human Being, Fed. Proc. **9**:371-372, 1950.

4. Snyderman, S. E.; Holt, L. E., Jr.; Carretero, R., and Jacobs, K.: Pyridoxine Deficiency in the Human Being, J. Clin. Nutrition **1**:200-207, 1953.

5. Snell, E. E.: Summary of Known Metabolic Functions of Nicotinic Acid, Riboflavin and Vitamin B_6, Physiol. Rev. **33**:509-524, 1953.

6. Fouts, P. J.: Nutritional Microcytic Hypochromic Anemia in Dogs Cured with Crystalline Factor I, Am. J. M. Sc. **199**:163-166, 1940.

7. Hawkins, W. W.; Lechow, B., and Evans, M. K.: Vitamin B_6 and Hematopoiesis in the Rat, Am. J. Physiol. **170**:155-159, 1952.

8. Stoerk, H. C., and Eisen, H. N.: Suppression of Circulating Antibodies in Pyridoxine Deficiency, Proc. Soc. Exper. Biol. & Med. **62**:88-89, 1946.

9. Axelrod, A. E.: Role of the Vitamins in Antibody Production (A Summation of the Author's Work to Date), Metabolism **2**:1-8, 1953.

10. Axelrod, H. E.; Morgan, A. F., and Lepkovsky, S.: The Fate of Tryptophane in Pyridoxine-Deficient and Normal Dogs, J. Biol. Chem. **160**: 155-164, 1945.

11. Dalgliesh, C. E.: Relation Between Pyridoxine and Tryptophan Metabolism, Studied in Rat, Biochem. J. **52**:3-14, 1952.

12. Chick, H.; El Sadr, M. M., and Worden, A. N.: Occurrence of Fits of Epileptiform Nature in Rats Maintained for Long Periods on Diet Deprived of Vitamin B_6, Biochem. J. **34**:595-600, 1940.

13. Daniel, E. P.; Kline, O. L., and Tolle, C. D.: Convulsive Syndrome in Young Rats Associated with Pyridoxine Deficiency, J. Nutrition **23**:205-216, 1942.

14. Bessey, O. A.; Adam, D. J. D.; Bussey, D. R., and Hansen, A. E.: Vitamin B_6 Requirements in Infants, Fed. Proc. **13**:451, 1954.

15. Hansen, A. E.; Wiese, H. F.; Adam, D. J. D.; Bussey, D. R., and Worsham, A. G.: Influence of Pyridoxine on Mineral Balance in Infant Maintained on a Convulsigenic Milk Preparation, Fed. Proc. **13**:460, 1954.

16. Hassinen, J. B.; Durbin, G. T., and Bernhart, F. W.: The Vitamin B_6 Content of Milk Products, J. Nutrition **53**:249-258, 1954.

17. Atkin, L.; Schultz, A. S.; Williams, W. L., and Frey, C. N.: Yeast Microbiological Methods for Determination of Vitamins, Indust. & Eng. Chem., Analyt. Ed. **15**:141-144, 1943.

18. Tomarelli, R. M.; Spence, E. R., and Bernhart, F. W.: J. Agricult. & Food Chem., to be published.

19. Hunt, A. D., Jr.; Stokes, J., Jr.; McCrory, W. W., and Stroud, H. H.: Pyridoxine Dependency: Report of a Case of Intractable Convulsions in an Infant Controlled by Pyridoxine, Pediatrics **13**:140-145, 1954.

Case Reports

THROMBOCYTOPENIC PURPURA OCCURRING WITH LARGE HEMANGIOMA

CAPT. EDWIN A. MEEKS (MC), U. S. Army
MAJOR JACK B. JAY (MC), U. S. Air Force
and
MAJOR GEN. LEONARD D. HEATON (MC),
U. S. Army

THE ASSOCIATION of thrombocytopenic purpura with large hemangiomas has been reported in seven infants.* Management of this condition has consisted of irradiation of the hemangioma, blood transfusions, and, in two cases, splenectomy. One author* states that splenectomy was probably not effective as a treatment of the thrombocytopenia in this syndrome. We wish to report a case in which splenectomy was followed by complete regression of the thrombocytopenia and hemangioma.

REPORT OF A CASE

A one-month-old white boy was admitted on April 17, 1953. He was born at full term, and delivery was spontaneous. The mother was normal and the pregnancy uncomplicated. His birth weight was 7 lb. 2 oz. The only abnormality noted at birth was a bluish discoloration, 2½ in. in diameter, involving the skin over the right deltoid area.

Circumcision was performed two days after birth without abnormal bleeding.

At 2 weeks of age the lesion on the right shoulder had become slightly elevated and was thought to be a cavernous hemangioma.

Three days before admission to this hospital, the lesion increased rapidly in size and the bluish discoloration was no longer confined to the initial lesion but extended anteriorly over the right chest and posteriorly over the scapula. In addition, many small petechiae were noted over the chest and abdomen (Fig. 1).

Submitted for publication April 19, 1955.

From the Pediatric Service (Captain Meeks), the Surgical Service (Major Jay), and Chief of Surgical Service (Major General Heaton), Walter Reed Army Hospital, Washington 12, D. C.

* References 1-6.

Fig. 1.—Large hemangioma with massive hemorrhage into and around lesion on admission to hospital.

The patient was admitted to another hospital, where his platelet count was 10,000 per cubic centimeter and the bleeding time was greater than 20 minutes. Two small blood transfusions were given, and cortisone therapy was started prior to transfer to our hospital.

Physical examination upon admission revealed a 9 lb. pale, irritable, white boy. There was a large, tense, purplish mass over the right shoulder surrounded by an ecchymotic area extending anteriorly to the right costal margin and posteriorly over the scapula. There were also numerous small ecchymoses and petechiae over the remainder of the body. The heart and lungs were normal. The abdomen was rounded. The liver edge was 1 fingerbreadth below the right costal margin, and the spleen was palpable 3 fingerbreadths below the left costal margin.

Course in Hospital.—Upon admission, our initial problem seemed to be to control further bleeding into the hemangioma. The platelet count was 21,000 per cubic centimeter and the hemoglobin was 8.1 gm.

Fig. 2.—Hemangioma of the right shoulder two weeks after splenectomy.

per 100 cc. The anemia was corrected with whole-blood transfusions, and cortisone, 6.25 mg. every six hours, was given orally in an attempt to control the bleeding. The bleeding time remained prolonged, but no further bleeding occurred during the first week.

One week after admission a transfusion of 80 cc. of platelet-rich serum was given through a polyethylene catheter. This was done for diagnostic purposes and treatment. We wished to raise the platelet count in order to control bleeding and also to learn whether the platelets were destroyed rapidly, which would normally occur if platelet antibodies were present.[7] The platelet count rose from 13,000 per cc. to 26,000 following this procedure, but we felt this was not a sufficient rise to allow any conclusions to be drawn.

The mass became more fluctuant, and it was aspirated in an effort to prevent necrosis of the skin. Only 30 cc. of bright red blood was obtained.

On the 10th hospital day there was sudden onset of bleeding from the hemangioma. The blood loss was rapid and in the following 14-hour period the infant was given 810 cc. of whole blood, an amount equal to approximately twice his blood volume. The bleeding was brought under control with absorbable gelatin sponge (Gelfoam) and pressure dressing.

Roentgen therapy was begun in an effort to reduce the size of the hemangioma and aid in the control of hemorrhage. Four treatments of 150 r each were given at weekly intervals for a total dose of 600 r. Radiation was given to a 7 cm. area through bulky pressure dressings.

The lesion increased in size during the radiation therapy. The hemangioma became infected, and there was marked proliferation of granulation tissue. The mass became so large that it caused the infant's head to rest upon the left shoulder. The progressive changes were suggestive of malignancy, but a biopsy revealed only granulation itssue.

The infant had a persistent anemia, even though there was little blood loss from the hemangioma. There was no evidence of hemolysis. The red blood cell fragility was normal. The Coombs test was negative. The total serum bilirubin was 0.3 mg., with a one-minute bilirubin value of 0.1 mg.

There was gradual enlargement of the spleen. The white blood cell count remained between 5,000 and 7,000 per cubic millimeter, even though the hemangioma was infected. A bone-marrow biopsy on July 28, 1953, revealed diffuse hyperplasia. The megakaryocytes were conspicuous, with granular cytoplasm and lobulated nuclei. The platelets were reduced in number.

The thrombocytopenia had shown no evidence of spontaneous remission after four months, and the picture of hypersplenism—anemia, thrombocytopenia, splenomegaly, and a hyperplastic bone marrow—was present. These two factors lead us to perform splenectomy. Cortisone therapy was begun two days preoperatively, and surgery was accomplished without excessive bleeding.

The spleen weighed 50 gm., and microscopic examination revealed large sinusoids with numerous hemosiderin-laden macrophages.

The platelet count rose gradually to a normal level on the fifth postoperative day. Coincident with

Fig. 3.—Hemangioma three months after splenectomy.

the return of a normal platelet count, there was sudden dramatic improvement in the hemangioma. The lesion began to shrivel and the granulating surface to heal. Figure 2 was obtained two weeks postoperatively. Prior to surgery, the mass was up to the level of the right ear and displacing the head to the left. Figure 3 shows the continued healing of the hemangioma three months after operation. The right shoulder joint was freely movable.

COMMENT

Seven cases of thrombocytopenia and large hemangiomata appear in the literature.† Management of these patients included radiation therapy, splenectomy, and blood transfusions. All but one had rather striking regression of the hemangioma at the time the platelet count returned to normal.

Bogin and Thurmond [4] reported the first patient treated with splenectomy. He states, "The response to splenectomy was slow and not dramatic; nevertheless, this procedure seemed to mark the turning point in the clinical picture, and we believe it was of benefit."

Weissman and Tagnon [6] reported splenectomy in a 9-month-old boy whose purpura was of two months' duration. There was no platelet response after six months. He presented a second case which had a spontaneous remission after five months and concluded that splenectomy was not effective in the management of the thrombocytopenia associated with hemangioma.

Our patient had a relatively small dose of radiation, 600 r, which was administered through bulky dressings soaked with blood. The hemangioma continued to enlarge during the radiation therapy. There was no rise in platelets until six days after splenectomy. Simultaneously with the rise in platelets the hemangioma began to regress. The occurrence of spontaneous remissions have been reported.[6] We feel that the return of normal platelet count was the result of splenectomy. The regression of the hemangioma seemed to be directly related to the return of normal platelets, as reported by Weissman and Tagnon.[6]

Although there are seven such cases reported, the coexistence of these two conditions, as suggested by Bogin,[4] may be coincidental.

The importance of making every effort to maintain these infants should be stressed, since all but one patient [5] had a favorable outcome.

SUMMARY

A case of hemangioma associated with thrombocytopenia in a one-month-old boy is reported. Splenectomy was performed after four months and was followed by a return of the platelet count to normal and dramatic regression of the hemangioma. The relationships of the two conditions are discussed.

Col. O. C. Bruton, Chief of Pediatric Section, Walter Reed Army Hospital, assisted in preparation of the manuscript and provided the photographs.

REFERENCES

1. Kasabach, H. H., and Merritt, K. K.: Capillary Hemangioma with Extensive Purpura: Report of a Case, Am. J. Dis. Child. **59**:1063, 1940.

2. Rhodes, A. W., and Berrelli, F. J.: Giant Hemangio-Endothelioma with Thrombocytopenic Purpura: Results of Roentgen Therapy, Am. J. Roentgenol. **52**:323, 1944.

3. Silver, H. K.; Aggeler, P. M., and Crane, J. T.: Hemangioma (Capillary and Cavernous) with Thrombopenic Purpura: Report of a Case with Observations at Autopsy, Am. J. Dis. Child. **76**:513, 1948.

4. Bogin, M., and Thurmond, J.: Hemangioma with Purpura, Thrombocytopenia and Erythrocytopenia, A. M. A. Am. J. Dis. Child. **81**:675, 1951.

5. Southard, S. C.; DeSanctis, A. G., and Waldron, R. J.: Hemangioma Associated with Thrombocytopenic Purpura: Report of a Case and Review of the Literature, J. Pediat. **38**:732, 1951.

6. Weissman, J., and Tagnon, H. J.: Syndrome of Hemangioma and Thrombocytopenic Purpura in Infants, A. M. A. Arch. Int. Med. **92**:523, 1953.

7. Harrington, W. J.; Sprague, C. C.; Minnich, V.; Moore, C. V.; Aulvin, R. C., and Dubach, R.: Immunologic Mechanisms in Idiopathic and Neonatal Thrombocytopenic Purpura, Ann. Int. Med. **38**:433, 1953.

† References 1-6.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Some Basic Problems in Atrophy of Infancy. L. Kulin, Ann. Pædiat. **183**:270 (Nov.) 1954.

In order to assess the therapeutic effect of climatic treatment in atrophic infants it is advisable to separate them into two major groups: 1. The actually diseased atrophic babies. 2. The babies who have been cured of the actual disease, i. e., the "intact" atrophic infants.

It should be emphasized that the "intact" atrophic children whose weight remained stationary to room temperature gained in the climatic ward although the energy quotient remained unchanged, while the diseased infants were able to put on weight only after their infection was cured.

In spite of the analogy of the disparity of body surface and weight in premature and atrophic infants, therapeutic use of humid warmth was not made for the following reasons:

1. The theory of overheating and the danger to life caused by it.

2. The rigid theory with regard to heat production of the active protoplasm (Flemming, Levine, Talbot, Benedict, Murlin, and co-workers).

3. Based on metabolic findings, the opinion was predominant that the basal metabolic rate (B. M. R.) is raised in atrophy.

4. That the raised B. M. R. was due to faulty cell activity.

Contrary to these opinions, the author followed the idea that the "intact" atrophic infants were not suffering from any such organic disease or from such a disturbance of metabolism responsible for the failure to put on weight. The cause for the inability to gain weight was thus sought for and found not in the endogenous but in the exogenous milieu.

From the Author's Summary.

The Effect of Pantothenic Acid on the Metabolism of Glucose. O. Olivi and E. Cheli, Clin. pediat. **36**:25 (Jan.) 1954.

Fasting sugar and pyruvic acid determinations were made on the bloods of five healthy boys before and after courses of five daily injections of pantothenic acid. No consistent changes were noted in the blood sugar content, but in 9 of the 10 cases, there was a lowering of the amount of pyruvic acid in the blood.

Higgins, Boston.

The Effects of Adenosine Triphosphate and of Adenosine Triphosphate Riboflavin on Weight Gaining in Infants. E. Cheli and O. Olivi, Clin. pediat. **36**:615 (Aug.) 1954.

Infants who had not been gaining in weight responded very satisfactorily to intramuscular injections of 5 to 15 mg. adenosine triphosphate daily over periods of 7 to 18 days; even better results followed the inclusion of 10 mg. riboflavin (lactoflavin) with each injection.

Higgins, Boston.

A Cereal Preparation Adapted for the Feeding of Infants. P. Avanzini, I. Bottinelli, and G. Sanolli, Minerva pediat. **6**:347 (May 15) 1954.

Farex is a proprietary cereal preparation, containing iron, calcium, phosphorus, dry yeast, vitamin D, and traces of copper. This product was found by the authors to be well tolerated by babies and especially useful for infants who have reached the age when they need other nutriments besides milk.

Higgins, Boston.

LIVER-PROTECTIVE SUBSTANCES AND THE KETONE BODY METABOLISM. M. MALASPINA, Minerva pediat. **6**:669 (Sept. 15) 1954.

The "liver-protective substances" used in this study were administered as a proprietary preparation (Liver Atox), containing for the most part the various B vitamins. Children, some of them well and others with a liver disorder, were put twice on a "butter" diet, the first time as a control and the second time with the Liver Atox. The day's excretion of acetone bodies was diminished about 15% as the result of the giving of the medication.

HIGGINS, Boston.

A STUDY OF THE GLUCOSE METABOLISM IN DYSTROPHIC INFANTS BY MEANS OF SUGAR TOLERANCE, EPINEPHRINE AND INSULIN TESTS. P. BRUSA, Minerva pediat. **6**:692 (Sept. 15) 1954.

Observations were made with 5 normal and 11 dystrophic infants. The carbohydrate metabolism was normal in many of the dystrophic infants. In the others, no consistently abnormal pattern existed. Some of the dystrophic infants had a low fasting blood sugar level. Insulin activity was at a low level in some and yet quite active in others; in these latter cases, there was probably a diminished absorption of glucose from the intestine. In the cases when the epinephrine test was weak, there must have been either an insufficient storage of glycogen in the tissues or an inability to convert glycogen into glucose.

HIGGINS, Boston.

METHYLANDROSTENDIOL IN THE TREATMENT OF DYSTROPHIC INFANTS. E. PENNATI, Pediatria **62**:220 (March) 1954.

A new hormone, methylandrostendiol, was found to be an excellent stimulus to growth in that 14 out of 16 dystropic infants showed gains in height and weight when it was given. The drug was also observed to bring to normal the serum protein picture and the blood cytology.

HIGGINS, Boston.

ACIDIFIED WHOLE MILK: THE ABSORPTION OF FAT AND ITS INFLUENCE IN THE IMMUNIZATION PROCESS. ANSELMO ALLUÉ DE HORNA, ASUNCIÓN IBARZ, and ROSA MOUNE, Rev. españ. pediat. **10**:327-354 (May-June) 1954.

The authors studied the absorption of fats in the use of acidified milk on an equal number of healthy and sick infants. The coefficient of absorption of fats was greater in both groups than in children given whole milk which was not acidified. The assimilation was not as good in the sick children at first, but they adapted themselves rapidly.

In newborn infants observed the number of infections were less than in the control neonates fed on whole nonacidified milk.

The details of the observations are given.

ALLEN, Santa Fe, N. Mex.

STUDIES IN FAT ABSORPTION IN THE INFANT WITH POWDERED ACIDIFIED MILK. M. SUAREZ and A. VELSCO, Rev. españ. pediat. **10**:335-368 (May-June) 1954.

This is a detailed study of the absorption of fats, using acidified powdered milk. Both fats and albumins were better absorbed when acidified powdered milk was used. Other milks used in the study were cows' milk, evaporated milk, and powdered milk without the addition of acid.

ALLEN, Santa Fe, N. Mex.

Hygiene; Growth and Nutrition; Public Health

MORBIDITY AND MORTALITY DATA FROM THE CLINIC FOR SICK CHILDREN OF TRIESTE DURING THE DECADE 1944-1953. B. EVA-DIACOMO and G. ROTTINI, Lattante **25**:454 (Aug.) 1954.

The advent of the antibiotic drugs and the change from wartime to peace conditions have caused a striking change in the types of illnesses and in the causes of deaths in Italian hospitals. Whereas the death rate in the Trieste Hospital in 1943 was 39%, it had gradually fallen to 9.2% in 1953. In 1944, acute nutritional or diarrheal disease was the cause of 32% of the deaths, 29% were caused by respiratory infections, and 26% by prematurity; in 1953, the percentages

were 5%, 2%, and 53%, respectively. Eleven of fifty-three patients with pulmonary tuberculosis died in the years 1944-1947; since the advent of streptomycin therapy, in 1948, only 2 of the 122 patients with pulmonary tuberculosis died. Although prematurity was the main cause of deaths in the hospital in 1953, the percentage of deaths among the admitted premature infants has fallen from 75% in 1947 to 22% in 1953.

HIGGINS, Boston.

GROWTH AND DEVELOPMENT. J. F. DE WIJN, Maandschr. Kindergeneesk. **22**:378 (Nov.) 1954.

The author presents a discussion of the most current methods for the assessment of growth and development with standard-growth diagrams. By a modification of Wetzel's grid a diagram was constructed enabling one to determine a child's development at a glance and to follow it longitudinally with respect to growth in height and increase of body weight. At the same time it enables one to judge the height-weight ratio at the age of the child in question. The diagram has been supplemented by an indication of the average age at which the first signs of sexual maturity are present.

The method is elucidated by examples:

(*a*) The longitudinal course of growth of a boy and a girl, until 15 and 16 years of age, respectively.

(*b*) The difference in the nutritional condition of 7-9-year-old children from two different social classes.

(*c*) The development of children from two Indonesian population groups, as compared mutually and with western standards.

A statistical justification is given of the diagram presented in this paper.

FROM THE AUTHOR'S SUMMARY.

Prematurity and Congenital Deformities

A FIELD STUDY OF RETROLENTAL FIBROPLASIA IN MARYLAND. HILDEGARD I. M. ROTHMUND, ROWLAND V. RIDER, and PAUL HARPER, Pediatrics **14**:455 (Nov.) 1954.

A field study of premature infants born in Maryland in 1952 showed that 5.5% of infants with a birth weight under 2000 gm. had residual lesions of retrolental fibroplasia. This was almost four times the incidence in the only other similar report in the literature. Approximately half of the cases identified possessed some useful vision in the better eye. The incidence of residual lesions within each weight group was highest in those infants with the shortest periods of gestation. The disease was two to three times more frequent in babies cared for in the five top-ranking hospitals than in the other 41 hospitals, and there was a direct relationship between the proportion of infants with residual lesions and the length of incubator care.

FROM THE AUTHORS' SUMMARY.

THE INCIDENCE OF CONGENITAL MALFORMATIONS: A STUDY OF 5,964 PREGNANCIES. RUSTIN MCINTOSH, KATHARINE K. MERRITT, MARY R. RICHARDS, MARY H. SAMUELS, and MARJORIE T. BELLOWS, Pediatrics **14**:505 (Nov.) 1954.

The plan is described of a prospective study of the outcome of 5964 pregnancies, with special emphasis on the relationship of factors in fetal environment to the incidence of abortions, stillbirths, neonatal mortality, and congenital malformations.

Data are presented on the over-all incidence of congenital malformations according to sex, race, weight at delivery, maternal age, and order of birth.

The incidence of congenital malformations among 5739 products of conception weighing over 500 gm. was 7.5%. The rate was 7.0% among infants born alive and surviving the neonatal period, 13.6% among antepartum deaths, 23.3% among intrapartum deaths, 29.6% among neonatal deaths, and 70.6% among deaths occurring between the ages of 1 and 12 months.

The following relationships in incidence rates among liveborn infants surviving the neonatal period were found:

1. The rate among males (8.4%) was half again as high as among females (5.5%).
2. Nonwhite infants had a higher rate (7.8%) than white infants (6.3%).

3. Infants weighing 2500 gm. or less had a higher proportion with defects (9.7%) than did those weighing over 2500 gm. (6.7%), although this difference occurred entirely among females.
4. Maternal age had no effect on the incidence of congenital malformations.
5. White infants of lower birth order had a lower rate (5.3%) than did those of higher birth orders (8.2%). No difference according to birth order was observed among nonwhite infants.

A system of classification of malformations is described and discussed. Incidence rates by organ-system groups are presented.

Less than one-half of the malformations found among liveborn infants were suspected or noted at birth.

Malformations of musculoskeletal system and skin were more frequent than malformations of other systems. Incidence rates by organ system groups are directly related to problems of diagnosis.

Of the malformed liveborn infants, 14.8% had more than one malformation and in 9.1% more than one system was involved. Of the malformed stillbirths and neonatal deaths, 66.0% had more than one malformation and in 51.1% more than one system was involved.

FROM THE AUTHORS' SUMMARY.

THE FEEDING OF THE PREMATURE INFANT. C. POTOTSCHNIG and A. VERGA, Minerva pediat. **6**:325 (May 15) 1954.

Experience with premature infants at the pediatric clinic of The University of Milan has led to the following recommendations. The premature infant should not be fed for the first 24 hours after birth, and sometimes not for 72 hours. Gavage is preferable with the very small premature infant and for others whose ability to nurse requires too much effort. When artificial feedings have been prepared with care and sterile precautions, they have proved as satisfactory as breast milk.

HIGGINS, Boston.

THE LONG-TIME PROGNOSIS OF PREMATURITY, BASED ON FIFTEEN YEARS' EXPERIENCE AT THE G. GASLINI CLINIC IN GENOA. E. DE TONI, Minerva pediat. **6**:525 (July 31) 1954.

Nine hundred two premature infants were admitted to the pediatric clinic between 1938 and 1952. Of these, 48.6% died in the hospital; the mortality rate was 53% before 1949 and 41% since that time. All infants with birth weights under 1000 gm. died; 75% of those weighing between 1000 and 1500 gm. died, while only 30% of those weighing over 2000 gm. died. Of 187 infants whose cases were followed after discharge from the hospital, 19 subsequently died of intercurrent infections. The proportions of children who were large-sized and small-sized for their age were not different in the children born prematurely from those born at full term. Of 167 children who had been born prematurely, 1 had superior intelligence, 150 normal intelligence, 12 low normal intelligence, and 4 were definitely feeble minded.

HIGGINS, Boston.

BLOOD TRANSFUSIONS AS PROPHYLAXIS AGAINST ANEMIA IN THE PREMATURE INFANT. C. POTOTSCHNIG and A. VERGA, Minerva pediat. **6**:537 (July 31) 1954.

A routine was followed in which each premature infant was given every 15 days a transfusion of 10 to 12 cc. per kilogram of body weight of fresh blood so long as the child remained in the hospital. Hemoglobin determinations and red blood cell counts were done monthly on each child until it was one year old. The results confirmed the favorable reports by French pedatricians that such a procedure aided in preventing the development of anemia. During the second half year, the red blood cell counts of these infants maintained a better level than did the hemoglobin.

HIGGINS, Boston.

Newborn

SOME OBSERVATIONS ON THE EXCRETION OF CORTICOIDS IN THE URINE OF CESAROTOMY AND SPONTANEOUSLY DELIVERED INFANTS DURING THE TWO FIRST POSTNATAL DAYS. URBAN FURUHJELM, Études néo-natal. **3**:125 (June) 1954.

The excretion of corticoids in the urine during the two first postnatal days was investigated in seven infants delivered spontaneously and six Caesarotomy infants. The values were low, a

mean value of 0.063 mg. during two days being obtained for the former and of 0.045 mg. for the latter. Per kilogram body weight, the corresponding values were 0.017 mg. and 0.014 mg. The degree of scatter of the values in the individual cases is comparatively marked, and the material is not comprehensive enough to allow any conclusions with regard to a possible difference between the two groups.

FROM THE AUTHOR'S SUMMARY.

THROMBOSIS PROPHYLAXIS WITH MARCOUMAR AND THE STATE OF THE CHILD. F. E. KÖNIG, T. REICH, and M. STEINBRÜCHEL, Schweiz. med. Wchnschr. **84**:440 (April 17) 1954.

The use of Marcoumar, a coumarine preparation, after birth to prevent thrombosis and embolism in the mother has no injurious effect on the nursling. The prothrombin content of the blood of such nurslings is not altered.

AMBERG, Rochester, Minn.

THE OSMOTIC RESISTANCE OF THE LEUCOCYTES IN THE NEWBORN INFANT. R. DE LUCA and G. LOMBARDI, Lattante **25**:13 (Jan.) 1954.

The resistance of the white blood cells to a 0.20% solution of sodium chloride was determined in a counting chamber under the microscope by the method of Storti. The polynuclear cells showed greater resistance and the mononuclear cells less resistance in the case of newborn infants than in the case of older babies. Tests were made daily on the newborn infants, and by the eighth day the resistance of both the polynuclear and the monocytic cells had reached the same level as in older babies.

These findings would seem to explain the frequent findings of bizarre white blood cell differential counts in the newborn infant.

HIGGINS, Boston.

NEONATAL MORTALITY AND THE NEONATAL FAILURE TO ADAPT. C. CAMMARELLA, Lattante **25**:65 (Feb.) 1954.

A listing of the neonatal deaths in Italy over a 10-year period (1941-1950) shows that 41.5% of the deaths were due to prematurity, 9.5% to specific illneses, 7.9% to birth injury, 7.4% to congenital malformations, and 0.6% to syphilis; 22.1% were due to congenital debility (not in the premature infant), 9.4% to asphyxia during and after birth, and 1.6% to ill-defined causes. The author reclassifies these last three groups under the heading, or category, "failure to adapt." This category would thus include morbid manifestations due to (1) intrauterine anoxia of the nervous centers, (2) demonstrable biochemical or morphological disorders, (3) clinical pictures, unidentifiable etiologically or pathologically, perhaps due to obstetrical shock or to inherent lack of capacity to adapt, and (4) adrenal cortex dysfunction.

HIGGINS, Boston.

ARRHYTHMIA IN THE NEWBORN INFANT. I. LONGO and A. VIANELLO, Lattante **25**:89 (Feb.) 1954.

An immature newborn infant, delivered by forceps after a long labor, showed a complete dissociated auricular-ventricular rhythm. The frequencies of the two rhythms varied, sometimes the auricular rate being faster and sometimes the ventricular rate being faster. The rhythm did not become wholly normal until after a period of two months. Treatment was by a belladonna preparation. Several electrocardiographic tracings are reproduced.

HIGGINS, Boston.

HISTOLOGICAL STUDY OF THE NERVOUS SYSTEM OF A NEWBORN INFANT WHO HAD DIED FROM HEMOLYTIC DISEASE. G. SANSONE and A. BRUSA, Minerva pediat. **6**:64 (Jan. 31) 1954.

An extensive histological study was made of the brain of a newborn infant who had died of kernicterus (the authors prefer the name "encephalopathy from hemolytic disease of the newborn"). The parents had an Rh incompatibility. It was found that there was always a parallelism between the intensity of the yellow color of the tissue and the histological deviations from normal. The lesions were not localized to the ganglion cells, but were much more diffuse, even involving the cerebral cortex.

HIGGINS, Boston.

CARBOHYDRATE METABOLISM IN THE NEWBORN INFANT. MARIO VERROTTI, Riv. clin. pediat. **53**:1 (Jan.) 1954.

Before examining certain morbid states caused by the alteration of the carbohydrate metabolism in the newborn infant, the author points out the normal physiological aspect of the glucide metabolism during the first days of life and insists upon the fact that newborn infants generally show a very low glycemic level, often below normal limits. A rich literature supports this affirmation, and the author's research underlies the fact that during the first days there is a remarkable hypoglycemic level which gradually decreases after the fourth day of life.

Next the author examines the causes of this particular feature of newborn glycemia, such as the sudden change in the way of feeding, the discontinuance of the intake of glucose from the maternal blood, the probable insufficiency of the complex glycoregulatory system at this time of life, and even a particular anatomic condition, hyperplasia of the insular system.

The author describes three particular syndromes to be ascribed to carbohydrate metabolism: (1) severe hypoglycemia proper to newborn children of diabetic mothers, (2) diabetes mellitus neonatorum, and (3) hypoglycemia of newborn children of hypoglycemic mothers.

Severe hypoglycemia of newborn children of diabetic mothers very often shows severe symptoms, such as those of hypoglycemic coma, irregular breathing, vomiting, cramps, and convulsions. Their glycemic level is remarkably low. The literature on the subject reports values much below the normal average, from 0.50 to 0.14 and 0.09. However, the administration of generous doses of sugar is often enough to correct these symptoms. Anatomopathological reports prove the existence of hypertrophy and hyperplasia of the endocrine portion of the pancreas. A content of insulin, 24 times higher than the normal one, has been sometimes found in this organ.

To confirm the dependence of severe newborn hypoglycemia on maternal diabetes, the author describes some laboratory research on animals and briefly discusses the probable pathogenesis of the syndrome. Next he describes a clinical experience of his own, the case of a 2-day-old infant with hypoglycemic coma (0.33 glycemia). The child was given 70 to 100 gm. of sugar per day and recovered after a fortnight's treatment. The clinical examination of the mother led to the conclusion that it was a case of latent diabetes. The author then spends a few words on the influence that a prediabetic state and latent diabetes may have on fetal glycoregulation.

After a detailed review of literature the author draws the conclusion that diabetes is extremely rare in newborn infants (only 11 severe cases reported all over the world). Such cases are the consequence of hypoplasia or of agenesis of the insular pancreatic tissue. The author describes the syndrome of hyperglycemia of newborn children of hypoglycemic mothers by reporting two clinical cases with the following symptomatology: (1) the child is deeply soporose, with dry skin, superficial and quick breathing, slightly enlarged liver, slight hypertonia, and sometimes convulsions; (2) there is a remarkable urinary content of glucose, the glycemic level is over 2%, the glucose and epinephrine curves and also Radoslaw's examination are the same as in cases of moderate hypoinsulinemia; (3) the clinical symptomatology improves with insulin therapy, glycosuria disappears entirely, and glycemia is reduced to normal levels within 15 to 20 days.

After the newborn symptomatology the author outlines the symptomatology of the pregnant mother, which is of no less importance for the exact interpretation of the symptoms, as follows: (1) during the last month of pregnancy, asthenia, headache, excessive perspiration; all these symptoms disappear after meals; (2) glycemic levels are constantly low, glucose and epinephrine curves and also Radoslaw's examination give a ready and prolonged insulin response.

Next the author dwells on the pathogenesis of the syndrome and draws the conclusion that there is a relationship between a maternal hypoglycemic state and the syndrome of the newborn child. The author maintains that the fetus of a hypoglycemic mother shows hyperfunction of the glycogenolytic system and hypofunction of the glycogenetic system; this might occur either by the natural reaction to a low intake of glucose from the mother or, considering the relationship between mother and fetus, a natural attempt to elevate the low maternal glycemic level. Consequently the child's metabolism of carbohydrates is, at birth, quite the opposite to what it should normally be; the glycogenetic properties are weak and even insufficient in comparison with the administration of carbohydrate substances, and the glycemic rate increases more or less rapidly, generating the morbid syndromes described in the two above-mentioned cases.

The author describes some of his own experimental researches on guinea pigs, with the aim of analyzing the pathogenesis. After having studied the carbohydrate metabolism of guinea pigs and of their offspring, strong doses of insulin (2 to 6 units a day) were given to some mothers during the whole time of pregnancy and to some only during the second half of the

time of pregnancy to provoke a daily hypoglycemic crisis. A certain percentage of the newborn animals showed remarkably high glycemia which gradually decreased during the first 10 to 20 days of life.

At the same time histopathologic researches were carried out in order to ascertain the particular hypoplasia of the insular tissue during the first days which gradually decreases and then disappears in 10 or 15 days. The author concludes by making a comparison between the spontaneous syndrome in man and the induced syndrome in animals, and he outlines some analogies between them.

FROM THE AUTHOR'S SUMMARY.

STUDIES ON LIPIDS, PROTEINS, AND LIPOPROTEINS IN SERUMS FROM NEWBORN INFANTS. STURE RAFSTEDT and BENGT SWAHN, Acta pædiat. **43**:221 (May) 1954.

With new micromethods, it has been possible to determine in 0.6 ml. serum the concentration of total and free cholesterol, phospholipids, and total lipids, and to perform electrophoretic separation of the protein fractions as well as of the various lipid fractions. Sera from blood of the umbilical cord and from capillary blood from 50 infants 1 to 6 days old were analyzed. The cholesterol, the total lipids, and the phospholipids increased 70% to 80% during the first few days of life. The marked increase in the lipids in the serum after birth was ascribable above all to the striking increase in the β-fraction, but also to the lipids in the fraction termed "chyomicrons." The α_1-fraction showed a moderate but statistically significant increase. During the first few days of life the α- and β-globulins showed a statistically significant increase, while the γ-globulin showed a statistically significant decrease. The albumin fraction did not change significantly.

FROM THE AUTHORS' SUMMARY.

SCLEREMA NEONATORUM: REPORT OF A CASE TREATED WITH CORTICOTROPIN (ACTH). GUNNAR SONDERGAARD and JOHANNES PETER NIELSEN, Acta pædiat. **43**:289 (May) 1954.

A case of sclerema neonatorum in a 4-week-old boy, treated with corticotropin (ACTH) with good effect, is reported.

FROM THE AUTHORS' SUMMARY.

SPONTANEOUS PNEUMOPERITONEUM IN THE NEWBORN INFANT. J. J. PIETERSE and J. SLOOFF, Maandschr. kindergeneesk. **22**:96 (March) 1954.

The authors give a description of two cases of spontaneous pneumoperitoneum in newborn infants.

FROM THE AUTHORS' SUMMARY.

PROBLEMS IN THE DIAGNOSIS OF HEMOLYTIC DISEASE OF THE NEWBORN INFANT. J. REEPMAKER and J. H. VAN BOLHUS, Maandschr. kindergeneesk. **22**:181 (June) 1954.

In more than 90% of the cases in which a newborn infant shows symptoms of hemolytic disease it is not difficult to make the diagnosis, because in addition to the clinical picture, the result of the serological investigations is conclusive.

In ABO incompatibility diagnostic problems are especially difficult to solve because the causal relationship between the latter and the former is not always well-established.

A survey is given of the principal clinical symptoms, laboratory data, and serological findings characteristic of hemolytic disease. The most important disorders occurring in the newborn period which must be differentiated from hemolytic diseases are discussed, and illustrative case histories are presented.

Some of these disorders, described only during recent years, are reported in more detail. Special attention is paid to the differential diagnosis of kernicterus and its various manifestations, which are certainly not due to blood group incompatibilty.

FROM THE AUTHORS' SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

ROLE OF THE PULMONARY VASCULAR BED IN CONGENITAL HEART DISEASE. J. FRANCIS DAMMAN JR. and WILLIAM H. MULLER JR., Pediatrics **12**:307 (Sept.) 1953.

In the normal human being systemic blood pressure is maintained at a high level by means of the high resistance offered to the flow of blood by the smaller systemic arteries and arterioles. In

contrast, pressure in the pulmonary circulation is maintained at a low level because of the relatively large size of the pulmonary vessels. In the fetal and newborn period pulmonary arteries resemble systemic arteries in that they have a small lumen and thick media. In this period pulmonary pressure and resistance are high. As these vessels gradually thin out and enlarge, resistance to pulmonary blood flow falls and, consequently, pulmonary blood pressure falls.

There is evidence to suggest that the fetal state of thick-walled, small-lumened pulmonary arteries is retained in instances in which the two circulations are joined, as in patients with a single ventricle, a large ventricular defect, and aortic septal defect, or a large patent ductus arteriosus. As the patient grows, resistance to pulmonary blood flow may do one of three things:

1. It may decrease. If the small pulmonary arteries develop normally and become thin-walled and large-lumened, pulmonary resistance will fall. More and more blood will be shunted into the lungs, and the patient will develop the signs and symptoms of cardiac decompensation.

2. It may remain the same. If the small pulmonary arteries retain their fetal characteristics, pulmonary resistance will remain elevated. A balance between systemic and pulmonary blood flow will be maintained compatible with a relatively normal life.

3. It may increase. If, because of secondary intimal changes, the pulmonary arteries become thicker-walled and smaller-lumened, pulmonary resistance will increase. Progressively less blood will be shunted to the lungs, and, finally, the shunt will reverse and become predominantly venous-arterial. The patient will develop the signs and symptoms of pulmonary stenosis, with increasing dyspnea and cyanosis.

Data from two groups of patients are presented to illustrate the importance of the pulmonary vascular bed. In the first group, early and severe symptoms of cardiac failure necessitated closure of a large patent ductus arteriosus early in life. The ductus was large, comparable to the size of the aorta; pressures from the aorta and pulmonary artery were similar, and the lung biopsies demonstrated that the lumens of the small pulmonary arteries were decreased in size and that the media were abnormally thick. In each instance closure of the ductus resulted in a cure.

In the second group the two circulations were joined by either a large ventricular defect or a single ventricle. Three patients were in cardiac failure due to excessive pulmonary blood flow. Pulmonary blood flow was decreased by the creation of pulmonary stenosis, the main pulmonary artery being narrowed 60% to 80%. The postoperative course in these three patients illustrates the value of the creation of pulmonary stenosis in instances in which the two circulations are joined by a large communication between the ventricles or the great vessels.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF THE SCHOENLEIN-HENOCH SYNDROME WITH ADRENOCORTICOTROPHIC HORMONE (A. C. T. H.) AND CORTISONE. M. G. PHILPOTT and J. N. BRIGGS, Arch. Dis. Childhood **28**:57 (Feb.) 1953.

Nine cases of the Schönlein-Henoch syndrome are presented in which treatment with corticotropin and/or cortisone was given. No dramatic results were encountered. The drugs did not prevent relapses in the condition or the onset of nephritis in three of seven cases; neither did they have any effect on the course of the nephritis. The authors were not convinced that the drugs were of any value in these cases.

KELLY, Milwaukee.

FOUR CASES OF ACUTE ACQUIRED HÆMOLYTIC ANÆMIA IN CHILDHOOD TREATED WITH A. C. T. H. B. S. ROSE and S. N. NABARRO, Arch. Dis. Childhood **28**:87 (April) 1953.

Four cases of acute acquired hemolytic anemia in children admitted at the General Infirmary, Leeds, within a period of 16 days, are described, and the possibility of an infective basis for this condition is discussed. The children ranged in age from 6 months to 8 years.

The effects of treatment with corticotropin on the course of the disease afford evidence that the underlying abnormal antibody reaction can be controlled if relatively large doses are given.

The variable course and progress of the disease and the need for an individual approach to cases are stressed.

KELLY, Milwaukee.

TWO CASES OF CONGENITAL MITRAL STENOSIS TREATED BY VALVOTOMY. B. D. BOWER, J. W. GERRARD, A. L. D'ABREU, and C. G. PARSONS, Arch. Dis. Childhood **28**:91 (April) 1953.

Two cases of congenital mitral stenosis, one with no other abnormality and the other with a coexistent patent ductus arteriosus, are described. The diagnosis was confirmed at operation and, in one case, also at necropsy.

Mitral valvotomy was performed in both cases.

Clinical diagnosis may be easy at times but difficult at others. Confirmation may be difficult.

The selection of suitable cases is important, since valvotomy should help the infant with a good left ventricle but cannot help the commoner type, which is due to unequal division of the common atrioventricular canal.

KELLY, Milwaukee.

COMPARATIVE STUDY OF CIRCULATING EOSINOPHILE LEVEL IN BABIES. JOAN M. BURRELL, Arch. Dis. Childhood **28**:140 (April) 1953.

Ninety-three full-term babies had daily eosinophile counts performed during the first week of life, before discharge from hospital with the mother.

Twenty-five of these babies had counts thereafter at weekly or twice-weekly intervals in their own homes. All blood samples were taken before feeding.

Comparison is made between the counts for these full-term babies and those for the 75 premature babies previously considered. Most full-term babies are born with some circulating eosinophiles, in contrast to the premature babies, who have no circulating eosinophiles at birth.

All infants making satisfactory progress show a gradual rise of eosinophiles until a high stable level is reached. In the case of premature babies this level is very high, but the full-term child has a lower stable level, although it is higher than the figure for adults.

KELLY, Milwaukee.

PULMONARY THROMBOSIS AND ITS ASSOCIATION WITH UNEXPECTED DEATH IN CHILDHOOD. JOHN L. EMERY, Arch. Dis. Childhood **28**:187 (June) 1953.

Fifteen cases of pulmonary vascular thrombosis with alveolar edema in children are described.

The cases occurred in four clinical groups: (*a*) severely debilitated neonates; (*b*) children severely ill for a long period; (*c*) children admitted to hospital with severe dyspnea, and (*d*) children found dead and referred to the coroner.

In children observed before death, symptoms of pulmonary thrombosis, which consist of pyrexia and dyspnea showing no response to antibiotic therapy, are frequently preceded by a history of loose stools or vomiting.

Care in maintaining fluid intake and tissue hydration in debilitated infants may prevent the onset of thrombosis, but we have no knowledge of the cause of the thrombosis in many cases.

When thrombosis has occurred, anticoagulation therapy would seem reasonable, in addition to the usual antibiotics.

KELLY, Milwaukee.

RUPTURE OF FETAL HEART DURING LABOR. R. A. MCINROY and ANNE L. M. GRAHAM, Arch. Dis. Childhood **28**:201 (June) 1953.

A case is described in which hemopericardium resulting from rupture of the right atrium during labor was found on necropsy to be the cause of death in a stillborn infant.

The rupture is considered probably to have been traumatic in origin, and factors concerned in the possible mechanism leading to this rare occurrence are briefly considered.

KELLY, Milwaukee.

ESTIMATION OF BLOOD PRESSURE IN CHILDHOOD WITH SPECIAL REFERENCE TO CHOICE OF STANDARD CUFFS. H. SAINSBURY, Arch. Dis. Childhood **28**:268 (Aug.) 1953.

An attempt has been made to ascertain to what extent the standard sizes of inflatable cuffs normally available are applicable to children of different ages, presuming that to obtain comparable readings they should enclose two-thirds of the upper arm of the children for whom they are intended.

Mean values for the sizes of children's arms at different ages are presented, and it was found that the 10 cm. cuff can be used for all children between the ages of 4 and 12 years. Wtih children below 4 years of age only the 5 cm. cuff will fit, and children over 12 years of age can take the adult cuff.

KELLY, Milwaukee.

FOURTEEN CASES OF IDIOPATHIC MYOCARDITIS IN INFANTS AND CHILDREN. HOWARD WILLIAMS, R. N. O'REILLY, and ALAN WILLIAMS, Arch. Dis. Childhood **28**:271 (Aug.) 1953.

Idiopathic myocarditis is a serious, frequently fatal, malady, occurring usually in the first two years of life.

The pathological lesion consists of widespread, but usually patchy, muscle damage with an associated inflammatory cell reaction.

The common clinical illness is a rapidly developing, usually fatal, cardiac failure, manifested by severe respiratory embarrassment, cyanosis, and tachycardia, with low or normal temperature, an enlarged heart and liver, and electrocardiographic symptoms of myocardial damage.

The acute form of the disorder is commonly mistaken for pneumonia, as respiratory embarrassment and cyanosis are the outstanding clinical features and cardiac enlargement is difficult, and frequently impossible, to detect clinically.

Treatment with digitalis and oxygen has been of very definite value in some patients.

The clinical and pathological evidence gives no clue as to the etiology of the disease.

KELLY, Milwaukee.

LEFT AURICULAR ENLARGEMENT IN ENDOCARDIAL FIBRO-ELASTOSIS. J. L. FREER and W. J. MATHESON, Arch. Dis. Childhood **28**:284 (Aug.) 1953.

Seven fatal cases of endocardial fibroelastosis are briefly described. In all, left auricular enlargement was demonstrated roentgenologically; consequently, the authors consider it to be a useful confirmatory sign in diagnosis.

KELLY, Milwaukee.

ERYTHROGENESIS IMPERFECTA OR CONGENITAL HYPOPLASTIC ANÆMIA (DIAMOND-BLACKFAN TYPE). O. D. FISHER and F. M. B. ALLEN, Arch. Dis. Childhood **28**:363 (Oct.) 1953.

A case of congenital hypoplastic anemia is reported. Previous treatment of the condition and the dangers of repeated blood transfusions are reviewed. The successful response to corticotropin and cortisone over a period of eight months is demonstrated and the mechanism of its effect discussed. The dangers of such therapy, if continued, are noted.

KELLY, Milwaukee.

RED CELL AND PLATELET SIZE OF MATERNAL AND FETAL BLUE WHALE BLOOD, WITH NOTE ON AGE AND GROWTH OF BALAENOPTERA MUSCULUS. ALFRED L. COPLEY, Études ńeo-natal. **2**:183 (Dec.) 1953.

Measurements of red cell diameters in maternal and fetal blue whale blood are recorded, using the double diaphragm (DD) method of oblique illumination and phase contrast microscopy. The values, obtained in air-dried unstained blood films, are similar to those of human blood.

The significance of red cell shape and size in connection with erythrocyte function and submergence of the whale is discussed. It is not clear whether a distinct adaptation of the physicochemical mechanism of the red cell proper or of the blood exists and what role may be assigned to the hypothetic accessory physicochemical lungs of the retia mirabilia in the whale circulation.

The morphology of the blue whale platelets is similar to that of human and other mammalian species. The observations on platelets are the first thus far reported in cetacean blood.

The occurrence of platelet agglutinates in blue whale blood suggests that the physiologic function of the platelet in this animal may be identical to that in other mammals, i. e., the initiation of hemostasis in blood capillary vessels.

The present status of knowledge of the growth and development of the blue whale is presented in order (*a*) to establish the approximate age of the individual female fetus of 5.8 meters of a mother whale of 22.3 meters and (*b*) to throw light on the surprisingly rapid development of fetus and infant of the largest animal in existence.

Recent ecologic findings on the growth and development of small-sized, toothed cetaceans, kept in captivity in an oceanarium, are discussed. Since the nursing period of the bottle-nosed dolphin was found to be one and a half years, the estimate, by several authors, of a seven-month nursing period of the blue whale infant needs reexamination.

FROM THE AUTHOR'S SUMMARY.

ARTERIOVENOUS ANEURYSMS OF LUNGS AND TELANGIECTASIA HAEMORRHAGICA HEREDITARIA (OSLER). H. WISSLER, Helvet. pædiat. acta **8**:111 (March) 1953.

The author describes the case of a 10-year-old boy with an arteriovenous fistula of the lung, the presence of which is proved by a systolic murmur and the typical tomographic picture. There is no cyanosis or other symptom of arteriovenous shunt. The mother is a member of a family with Osler's disease.

FROM THE AUTHOR'S SUMMARY.

THE RELATION OF THE THYMUS TO SOME FACTORS INVOLVED IN BLOOD COAGULATION AND HEMOSTASIS. G. GELLI and L. SACCO, Minerva pediat. **5**:922 (Oct. 31) 1953.

Four cubic centimeters of a water extract of the thymus gland (Timoforte-Richter) was given to eight normal children by intramuscular injections. It was established that these injections increased the blood platelet counts and shortened the prothrombin time.

HIGGINS, Boston.

PROPOSED NEW TECHNIQUE FOR EXSANGUINOTRANSFUSION. R. COCCHI, Riv. clin. pediat. **51**:385 (Nov.) 1953.

A new technique for the exsanguinotransfusion is described; this method reduces the trauma and allows a larger employment of this treatment.

FROM THE AUTHOR'S SUMMARY.

CASE OF HEMANGIOBLASTOMA OF THE SPLEEN AND LOWER EXTREMITIES. F. RAGAZZINI, Riv. clin. pediat. **51**:512 (Dec.) 1953.

The author describes a rare case of cystic congenital hemolymphangioblastoma localized in the lower extremities and in the spleen; moreover, he discusses the differential diagnosis in this case and outlines the histological picture and the therapeutic attempts, which were carried out successfully.

FROM THE AUTHOR'S SUMMARY.

VALUE OF RETROGRADE AORTOGRAPHY IN CONGENITAL CARDIOPATHIES AFTER OPERATION. AGUSTIN CASTELLANOS, OTTO GARCÍA, and RAUL PEREIRAS, Arch. med. inf. **22**:141 (July-Sept.) 1953.

Attention is called to the importance of aortography in studying the permeability of the anastomosis performed in the Potts-Smith-Gibson, Blalock-Taussig, and other vascular operations, and in the postoperative study of persistent ductus arteriosus, coarctation of the aorta, and other angiocardiopathies.

In some cases of multiple malformations, such as the tetralogy of Fallot, in which the aorta overrides the ventricular septum, the dextroangiocardiogram gives us rather diffuse images, owing to the fact that some of the opaque substance goes into the stenotic pulmonary artery and the anastomosis is thus not well defined; besides, since the aorta overrides the septum, the radiopacity of the aorta is less pronounced, because the blood from the right ventricle is mixed with that of the left ventricle, which is not radiopaque; all these factors contribute to making it impossible to obtain a good image no matter what position is used.

A review of the different ways in which superior and inferior aortograms (thoracic and abdominal, respectively) may be made is made, and a discussion of the best means of making the aorta and its branches radiopaque in order to check on the success of the permeability of surgical anastomosis is given.

A series of films is presented which clearly shows the great usefulness of aortograms in the study of surgical procedures that tend to raise the blood volume of the pulmonary circulation.

FROM THE AUTHORS' SUMMARY.

ENDOCARDIAC FIBROELASTOSIS (ENDOCARDIAL SCLEROSIS): ANATOMICAL AND CLINICAL PRESENTATION OF SIX CASES. G. VOUSSURE and P. DROCHMANS, Acta pædiat. belg. **7**:241, 1953.

Nine cases of endocardial sclerosis in children aged from 2 months to 3 years (and one 12 years of age) are presented. One child survived. The presenting symptoms were circulatory failure and massive cardiac enlargement without toxic, infectious, or other cause for such changes. The etiology is unknown, and symptomatic treatment with digitalis and diuretics produced only temporary relief.

The pathological findings in the six cases in which autopsies were performed were endocardial thickening, particularly of the left ventricle, with some fibrotic changes of the myocardium.

The one surviving child (3 years old) had recurring signs of decompensation. He was admitted with accompanying bronchitis and responded to antibiotics and digitalis.

A total of some 300 cases have been reported in the literature up to the writing of this article.

GLASER, Jerusalem.

TREATMENT OF RHEUMATIC CARDITIS WITH CORTICOTROPIN AND CORTISONE. S. VAN CREVELD and F. KUIPERS, Maandschr. kindergeneesk. **21**:41 (Feb.) 1953.

The prognosis of rheumatic carditis in children grows worse as the number of relapses increases. Nowadays, the mortality from rheumatic fever is mainly that of its sequelae, i. e., valvular lesions. Apart from prevention of relapses by prophylactic methods, a better prognosis may be obtained by early treatment of rheumatic carditis with corticotropin or cortisone. On the basis of a survey of the literature, hope seems to be justified that early treatment with adequate doses can prevent persistent damage, such as valvular lesions, in a fair number of cases.

Observations on seven patients treated with cortisone are reported. Two of the children died. In two others, however, a fatal result was prevented by the therapy. All children showed evidence of a valvular lesion after treatment had been completed, although therapy had been instituted within two weeks after the first clinical signs of cardiac involvement in rheumatic fever.

The importance of a prolonged electric systole (Q-T_c) in evaluating the activity of rheumatic carditis is mentioned.

FROM THE AUTHORS' SUMMARY.

MEGALOBLASTIC ANEMIA AND VITAMIN B_{12}. T. D. STAHLIE, Maandschr. kindergeneesk. **21**:396 (Dec.) 1953.

A case of megaloblastic anemia in an infant who responded well to small amounts of both intramuscular and oral vitamin B_{12} is reported. The baby was completely cured. The pathogenesis in this case was not clear.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat, and Ear

TRACHEOTOMY IN CHEST INJURIES. HANS VON LEDEN, Illinois M. J. **104**:181 (Sept.) 1953.

In serious chest injuries, a tracheotomy is often a life-saving procedure. Good results can be expected only if a patent airway is restored in time; surgical intervention cannot be expected to change the prognosis when the patient is in extremis or after asphyxia or cardiac exhaustion, having passed beyond the stage of possible recovery.

A correctly performed tracheotomy is a harmless procedure and carries no additional risk for the patient with respiratory obstruction. Adequate postoperative care is essential for the maintenance of a patent airway. Tracheobronchial secretions must be aspirated at frequent intervals, and the formation of blood clots or crusts may call for a thorough tracheobronchial toilet or bronchoscopic expiration. Teamwork is essential in the treatment of crushing chest injuries. Respiratory obstruction with pulmonary complications and asphyxia can usually be avoided if a laryngologist, familiar with the anatomy and physiology of the respiratory tract, is permitted to supervise the problem of airway maintenance.

FROM THE AUTHOR'S SUMMARY.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

IDIOPATHIC CELIAC DISEASE: I. MODE OF ONSET AND DIAGNOSIS. DOROTHY H. ANDERSON and PAUL A. DI SANT'AGNESE, Pediatrics **11**:207 (March) 1953.

The acute phase of idiopathic celiac disease was studied in 58 patients. The criteria for selection of these cases are stated.

The frequency and severity of gastrointestinal symptoms in siblings and other relatives appear to exceed expectation, unless the disease is familial.

In the majority of patients studied, symptoms began before the age of 6 months, in 14, at birth. Vomiting was a frequent prodromal symptom. Breast feeding for more than two months was shown to delay the onset of diarrhea. The early onset of symptoms in the present series is believed to be related to the prevalence of formula feeding from early infancy in New York.

Severe retardation in growth of the skull was common and occurred at an earlier age than retardation in height. This at times led to disproportion between measurements for total body length and head circumference. Ultimate head measurements were normal.

The following laboratory procedures were performed in the patients under consideration and their results recorded: pancreatic trypsin and amylase estimation on duodenal drainage, glucose tolerance tests, fecal fat determination, total serum protein, serum carotene, and vitamin A levels, and vitamin A absorption test. The diagnostic usefulness of these procedures is discussed.

Various diseases of infancy which may lead to an erroneous diagnosis of idiopathic celiac disease are discussed.

FROM THE AUTHORS' SUMMARY.

A PSEUDOTUMOR OF THE COLON IN A CHILD. L. SALMI and F. BRILLANTI, Clin. pediat. **35**:911 (Dec.) 1953.

A 10-year-old boy had had for a year periods of abdominal pain, constipation, abdominal swelling, and loss of weight. A diagnosis of obstruction of the transverse colon was made. At operation, the seat of the obstruction was found and about one-half of the colon removed. Histological examination revealed a nonspecific obliterating granuloma of the colon.

HIGGINS, Boston.

THE FAILURE TO PASS MECONIUM. W. GALLUZZI, Lattante **24**:875 (Nov.) 1953.

If a new-born baby has not passed meconium by the 20th hour after birth, an intestinal obstruction is probable. The x-ray technique for establishing a diagnosis and for localizing the obstruction is discussed in this paper. In most cases, sufficient air has been swallowed to afford a natural contrast medium. In some cases, a barium enema may be necessary in order to obtain a more accurate analysis of the pathology.

HIGGINS, Boston.

TWO CASES OF CYSTIC FIBROSIS OF THE PANCREAS. G. CAFFERINA and C. ZUNIN, Minerva pediat. **5**:1080 (Dec. 15) 1953.

Three cases of cystic fibrosis of the pancreas in infants are reported, two of which were confirmed by autopsy findings.

HIGGINS, Boston.

Nervous Diseases

FURTHER OBSERVATIONS ON FAMILIAL DYSAUTONOMIA. CONRAD M. RILEY, ALFRED M. FREEDMAN, and WILLIAM S. LANGFORD, Pediatrics **14**:475 (Nov.) 1954.

Studies of familial dysautonomia by a team made up of a pediatrician, a neurologist, speech therapists, psychiatrists, psychologists, and a psychiatric social worker have been presented in summary form.

1. Facts supporting the theory that this is a condition of genetic origins are enumerated. They are compatible with its being transmitted by an autosomal recessive gene.
2. Evidence of disturbance of statural growth, with frequent significant dwarfing, is presented.
3. Postural hypotension as a regular part of the syndrome is demonstrated.
4. Data showing the variable neurological abnormalities are included.
5. The frequency of disturbance of speech, but not of language organization, is reported.

6. Psychological testing suggests a deterioration with advancing years in dealing with concrete tests but no significant disturbance in abstract thinking.

7. At the psychosocial level, inadequate adjustment to daily life is seen in all patients. This difficulty is reflected in varying degree by emotional disturbance in the parents. A schematic concept of the dynamics is offered.

8. Drug treatment of the acute crisis is discussed, and a plan for daily management of such cases is projected.

9. Avenues for further investigation are briefly mentioned.

FROM THE AUTHORS' SUMMARY.

A NEUROLOGICAL SYNDROME IN INFANTS RECOVERING FROM MALNUTRITION. E. KAHN, Arch. Dis. Childhood **29**:256 (June) 1954.

Among 1000 cases of infantile malnutrition admitted to Baragwanath Hospital there were 8 with characteristic neurological disturbances. These consisted of tremors, similar to those seen in Parkinsonism, cogwheel rigidity and lead-pipe rigidity of the extremities, and exaggerated tendon reflexes. Some infants also showed myoclonus, opisthotonos, and insomnia. These manifestations developed at a time when there were already signs that the nutritional state of the patients was improving. The syndrome disappeared entirely, or nearly so, within a few weeks or months of onset.

KELLY, Milwaukee.

MONILIASIS OF THE CENTRAL NERVOUS SYSTEM IN A CHILD WITH RECOVERY. WILLIAM EMDIN, South African M. J. **28**:868-871 (Oct. 9) 1954.

The authors report a case of central nervous system moniliasis in a 4-year-old boy. Candida albicans was removed from the hyperkeratotic lesion on the upper lip and from the cerebrospinal fluid. Marked improvement resulted following intravenous administration of methylrosaniline chloride (gentian violet). Its use is recommended especially where central nervous system involvement is present.

MCGUIGAN, Evanston, Ill.

AN ELECTROENCEPHALOGRAPHIC STUDY OF CHILDREN WITH MINOR LIVER DYSFUNCTION. S. NORDIO and F. PISTONE, Clin. pediat. **36**:563 (Aug.) 1954.

Electroencephalograms were done on 15 children with minor liver dysfunction. The tracings were normal in three cases. In the other 12 cases, various abnormal findings were found, especially dysrhythmia, and, on hyperventilation, increased voltage. These findings are interpreted as expressing a state of immaturity, excitability, and lability of the nervous system of the diencephalon. The findings are somewhat similar to those found in patients with allergic or with neurotic conditions. Thus the opinion is expressed that the encephalitic changes in this group of patients are functional and not due to a metabolic disorder.

HIGGINS, Boston.

RESULTS OBTAINED BY THE ORAL ADMINISTRATION OF TETRACYCLINE TO TWELVE PATIENTS WITH PURULENT MENINGITIS DUE TO VARIOUS ORGANISMS, AND SUPERIMPOSED ON TUBERCULOUS MENINGITIS IN THE COURSE OF TREATMENT. A. DEGLI ESPOSTI, Clin. pediat. **36**:627 (Aug.) 1954.

Tetracycline, given orally, has proved very successful in the clearing up of 12 cases of purulent meningitis in from three to seven days. These patients were receiving treatment for tuberculous meningitis at the time that the pyogenic infection occurred. Previously, successful results had been obtained with other antibiotic drugs, but only after a much longer period of treatment.

HIGGINS, Boston.

PSEUDOMONAS AERUGINOSA (B. PYOCYANEUS) MENINGITIS. B. JANSSEN, Maandschr. voor kindergeneesk. **22**:367 (Nov.) 1954.

The author describes a case of pyocyaneous meningitis in a newborn infant, ending fatally and treated with streptomycin and polymyxin B. The author reviews the relevant literature and discusses the pathogenesis and course of this disease and its treatment. He especially stresses the importance of the therapy with polymyxin B or E, intrathecal administration being an essential factor.

FROM THE AUTHOR'S SUMMARY.

Psychology and Psychiatry

EXCESSIVE INFANT CRYING (COLIC) IN RELATION TO PARENT BEHAVIOR. ANNA H. STEWART, I. H. WEILAND, ALLAN R. LEIDER, C. MAUGHAMS, THOMAS H. HOLMES, and HERBERT S. RIPLEY, Am. J. Psychiat. **110**:687 (March) 1954.

Crying, according to the conclusion of the authors, is a response to tension arising within the infant as a result of unmet needs or from inappropriate external stimulation. Eighteen infants representing 13 families were studied from the viewpoint of infant-parent relationship. Tension in the baby was found to vary directly with tension and incompetency of one or both parents.

JAHR, Omaha.

THE EFFECTS OF INFANTILE EXPERIENCES UPON ADULT BEHAVIOR IN ANIMAL SUBECTS. PHILIP F. D. SEITZ, Am. J. Psychiat. **110**:916 (June) 1951.

Experimental manipulation of litter size was used as a method of inducing variation in maternal care and nurture during suckling periods of rats. One hundred twenty newborn rats were divided into two groups, one being reared in litters of six, the other in litters of twelve. The rats of the latter group were exposed to considerably greater frustration and competition in connection with maternal care and nurture than the rats of the first group.

At maturity tests were done to determine whether the infantile experience variables had resulted in behavioral differences between the two groups, with the following results:

1. Male animals of small litters weighed significantly more than males from large litters, a difference that continued far into adulthood. They ate more and went after food more vigorously when hungry.

2. The animals from large litters hoarded significantly more food in adulthood. They were also more successful in competition for food during adulthood than the small-litter animals.

3. Small-litter animals reacted to novel experiences with less anxiety and more exploratory behavior in adulthood.

4. The large-litter animals exhibited significantly more mating behavior toward a female in heat during adulthood. They were more furious, bit more, struggled more when handled, and reacted with greater startle to new stimuli.

The results of the investigation, the authors conclude, support the hypothesis that experiences during infancy of a mammal can influence subsequent behavior of the organism throughout life.

JAHR, Omaha.

PAROXYSMAL FUSSING IN INFANCY, SOMETIMES CALLED "COLIC." MORRIS A. WESSEL, JOHN C. COBB, EDITH B. JACKSON, GEORGE S. HARRIS JR., and ANN C. DETWILER, Pediatrics **14**:421 (Nov.) 1954.

The literature on "infantile colic," or "paroxysmal fussing," is reviewed. The frequent occurrence of a regular evening fussy period in two groups of infants is reported as indicative that this is a normal physiological event of the first few weeks of life.

The longitudinal records of 98 infants who were study subjects of the Yale Rooming-In Project were analyzed with respect to incidence, duration, and severity of "paroxysmal fussing." Forty-eight of the infants were classified as "fussy" and fifty as "contented."

The "fussy" babies typically began to have their paroxysms in the second week of life and ceased to have them at about eight weeks. Almost all of them were more fussy in the evening hours than in the morning. The rationale of various methods of treatment is discussed.

The "fussy" group was similar to the "contented" group as regards details of feeding, birth weight, weight gain, sex, educational level of the mother, and family history of allergy.

Of the 48 "fussy" infants, family tension was judged to be an important contributing cause in 22 cases, allergy in 6 cases, both allergy and family tension together in 9 cases; in 11 cases there was no apparent cause.

"Paroxysmal fussing," or "infantile colic," is possibly one of the earliest somatic responses to the presence of tension in the environment. The particular degree to which any infant reacts is probably determined by constitutional factors.

FROM THE AUTHORS' SUMMARY.

"Mysoline" in the Treatment of Recalcitrant Idiopathic Major Epilepsy in Mentally Defective Children. Thomas A. Couston, Arch. Dis. Childhood **29**:323 (Aug.) 1954.

Six cases of recalcitrant idiopathic major epilepsy in mentally defective children have been treated with Mysoline over a period of 11 weeks. All six cases had received intensive anticonvulsant therapy previously with other drugs. Each case showed remarkable improvement in a very short period with freedom from side-effects; in one case improvement was noted during the first seven days' treatment. The improvement in all cases took two forms: (1) personality changes and (2) decrease in the number of episodes of grand mal.

The personality changes took the form of great improvement in the general well-being of the patient, with increased mental and physical activity and increased powers of concentration with improvement in sociability and performance.

It appears that Mysoline has an important place in the treatment of recalcitrant idiopathic major epilepsy in mentally defective children, especially in those showing well-marked physical and mental deterioration.

Kelly, Milwaukee.

Diseases of Genitourinary Tract

Epidemic Acute Glomerulonephritis at Red Lake. Herman Kleinman, Minnesota Med. **37**:479 (July) 1954.

An epidemic of acute glomerulonephritis in the Red Lake Reservation in northern Minnesota is reviewed. In a community of about 3000 people, 63 cases of acute glomerulonephritis occurred. All cases were in children.

A characteristic pyoderma was present with nephritis in about two-thirds of the cases. A group A nontypeable beta hemolytic Streptococcus seemed to be the responsible organism.

A mass prophylaxis program using a long-acting penicillin preparation succeeded in practically obliterating the Streptococcus within a three-week period. The occurrence of nephritis was likewise abruptly terminated.

Stoener, Minneapolis.

Organic Urinary Incontinence in Children. Donald F. McDonald, Northwest Med. **53**:1009 (Oct.) 1954.

Treatment of organic urinary incontinence in children depends upon accurate urologic diagnosis. A classification of causes of organic urinary incontinence is presented.

Medical treatment with parasympathomimetic drugs and methantheline (Banthine) and Dibenzyline are discussed. Best long-term results derive from well-planned and well-executed conservative surgical treatment. Newly devised operative techniques which offer a much better prognosis for life and improved bladder function are discussed.

Docter, Seattle.

Idiopathic Renal Acidosis in Infancy. I. J. Carre, E. S. B. Wood, and W. C. Smallwood, Arch. Dis. Childhood **29**:326 (Aug.) 1954.

Seventeen children with idiopathic infantile renal acidosis were diagnosed in the children's hospital.

Alkali in high dosage was used in their treatment but did not give any better results than have been reported with more moderate dosage. Anemia, which was often hypochromic, developed under treatment with alkali in some. Its possible etiology is discussed.

Biochemical studies suggest that idiopathic infantile renal acidosis may at times be associated with azotemia and hypercalcemia. Aminoaciduria was recorded in only one case.

The follow-up of 13 children whose treatment has been discontinued for periods of from four months to four and one-half years suggests that among survivors the disorder leaves no serious ill effect.

A search for extrinsic factors that might cause or precipitate the disease was unfruitful. Prolonged medication with magnesia magma (milk of magnesia) could not be incriminated.

Kelly, Milwaukee.

CONGENITAL OBSTRUCTION OF THE BLADDER NECK. EDWARD STUCKEY, M. J. Australia **2**:321-323 (Aug. 28) 1954.

Neurogenic bladder-neck obstruction stenosis and congenital valves in the prostatic urethra are the common types of bladder-neck obstruction. Treatment is generally satisfactory if diagnosis is not too long delayed.

McGUIGAN, Evanston, Ill.

FAMILIAL GLYCOSURIA AND AMINO-ACIDURIA. E. JUILLARD and C. PIGUET, Ann. pædiat. **183**:257 (Nov.) 1954.

The authors describe two cases of glycosuria and aminoaciduria in a brother and sister. Absence of disturbances in the P-Ca metabolism and of radiological signs of rickets and the fact that the mental and physical development of the children was normal made it possible to exclude, at least for the moment, the possibility of the syndrome of Fanconi-de-Toni-Debre. Dent has shown that this syndrome may make its appearance only in adult age, having remained in an occult stage during childhood. The possibility can therefore not be excluded that the two children are suffering from an early stage of this syndrome which might fully develop at a later time. It remains to be seen whether the illness will remain in its present stage or develop into a classic disease.

FROM THE AUTHORS' SUMMARY.

CHROMATOGRAPHY IN BASAL AMINOACIDURIA AND IN ALKAPTONURIA. P. CAREDDU, J. PUGIONI, and C. VULLO, Ann. ital. pediat. **7**:299 (Aug.) 1954.

The author describes a case of alkaptonuria and calls the attention to an alteration of the tubular reabsorption of amino acids.

FROM THE AUTHORS' SUMMARY.

THE THERAPEUTIC USE OF CATION EXCHANGE RESINS IN NEPHROTIC EDEMA OF CHILDREN. I. SALA and I. FRIED, Lattante **25**:385 (July) 1954.

Seven separate observations were made with edematous nephrotic children in which a cation exchange resin saturated with 70% ammonium and 20% potassium radicals was fed in daily divided doses of 20 to 40 gm. over a period of one to four weeks. In one observation the resin cation saturation was by 20% potassium and 80% hydrogen.

The therapeutic results were good in four and good but only transitory in one of the seven clinical tests. With the disappearance of the edema, striking changes were noted in the plasma electrolytes, especially a lowering of the sodium content and of the alkali reserve.

Because of the tendency to acidosis, frequent accurate plasma electrolyte determinations are necessary during cation resin exchange treatments.

HIGGINS, Boston.

DETERMINATIONS OF AMINO ACIDS IN THE URINES OF HEALTHY BOYS TWO TO TWELVE YEARS OLD. S. LO BIANCO, Lattante **25**:449 (Aug.) 1954.

The percentages and types of amino acids found in the urines of 40 healthy boys, 2 to 12 years of age, were more like the findings in adult urine than in the urines of children under 2 years.

HIGGINS, Boston.

Diseases of Ductless Glands; Endocrinology

PROLONGED CORTISONE AND HYDROCORTISONE THERAPY. CARL E. ARBESMAN and NORMAN B. RICHARD, J. Allergy **25**:306 (July) 1954.

Cortisone or hydrocortisone was used in a group of 75 patients for periods of one week up to four years; in 16 of them for more than two years. There were rest periods of some of the patients during which time corticotropin (ACTH) was given. Sixteen of the patients were under 20 years of age, five of them under 10 years. Sixty-three of the patients were asthmatics.

A large dose was given initially; this was gradually reduced to a maintenance dose. The daily maintenance dose for cortisone was between 50 and 75 mg., for hydrocortisone between 40 and 60 mg. The most frequent side-effect was edema, in spite of low-sodium diets and supplemental potassium.

The drugs were used only when other usually effective methods had failed.

The authors feel that both drugs can be used for prolonged periods with success. Hydrocortisone is at least equally as effective as cortisone. The comparable effective dose of hydrocortisone is approximately two-thirds that of cortisone.

"The proper maintenance level of dosage is more important than the choice between cortisone and hydrocortisone."

HOYER, Cincinnati.

CONGENITAL HYPERPLASIA OF THE ADRENALS WITH ADDISON MANIFESTATIONS. ROBERT DEBRE, P. MOZZICONACCI, R. MANDE, B. LEVERQUE, and M. BERKMANN, Presse méd., Supp. 86, p. 1767, Dec. 25, 1954.

The syndrome of congenital hyperplasia of the adrenals is characterized by a combination of hyperandrogenism signs with mineralocorticoid insufficiency. This syndrome may be readily diagnosed and should be suggested in the case of vomiting and gradual denutrition in a newborn infant. Hyperandrogenism is immediately recognized in the male newborn infant and a little later in the female. Mineralocorticoid insufficiency is demonstrated in both sexes by a high concentration of chlorine and sodium in the urine.

As a consequence of this urinary waster in chlorine and sodium, there are to be observed such electrolytic disorders as hyponatremia, hypochloremia, and also hyperkaliemia. Furthermore, hyperandrogenism is manifested by a rise in the level of the urine 17-ketosteroids. The interest of the case reported here is to emphasize the possibility of combatting these metabolic disorders with the use of desoxycorticosterone and cortisone and of obtaining in this way a rather long survival of the young patients.

FROM THE AUTHORS' SUMMARY.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

LEONTIASIS OSSEA, SLIPPED EPIPHYSES, AND GRANULOSA CELL TUMOR OF TESTIS WITH RENAL DISEASE. JONATHAN COHEN and ISRAEL DIAMOND, A. M. A. Arch. Path. **56**:488 (Nov.) 1953.

This is a case report of a 21-year-old man who presented the following principal pathological lesions: hypoplastic kidneys; chronic pyelonephritis; leontiasis ossea; hyperparathyroidism, slipped epiphyses, and osteitis fibrosa secondary to renal disease; granulosa cell tumor of the testis; congenital megaloureter and hydronephrosis possibly secondary to ganglion cell deficiency, and aortic coarctation. A seven-year study of his clinical course and serum electrolyte pattern is summarized.

CHAN, San Francisco.

HYPOTONIA. R. T. LIDGE, J. Pediat. **45**:474-477 (Oct.) 1954.

Lidge describes a 16-month-old white girl with hypotonia. The salient features were (1) normal muscle power but poor tone, (2) normal reflexes, (3) joint relaxation with subluxation of the knees, (4) hypermobility, (5) normal electrical studies, (6) normal bone x-rays. He discusses the differential diagnosis.

MACDONALD, Pittsburgh.

VERTEBRAL COLLAPSE AFTER CORTISONE THERAPY. J. LUDER, Great Ormond St. J., No. 7, pp. 15-21, June, 1954.

The occurrence of vertebral collapse in four cases treated with cortisone over prolonged periods leads to the recommendation that all cases under prolonged cortisone therapy should have periodic x-rays of the spine.

The cause is thought to be a disturbance of the bone matrix with resultant nitrogen loss. A trial of steroid hormones is suggested.

MCGUIGAN, Evanston, Ill.

THOMSEN'S MYOTOMA CONGENITA. R. ROBLER, Helvet. paediat. acta **9**:351 (Oct.) 1954.

The clinical picture of myotonia congenita Thomsen has been observed in two siblings (5½ and 15½ years old), both of whom showed classical symptoms of the disease. Besides the fact that myotonia congenita Thomsen rarely occurs, it also deserves the interest of pediatricians because it can be recognized in early childhood. The symptomatology in infants and young children has been especially emphasized.

FROM THE AUTHOR'S SUMMARY.

AN UNUSUAL SEQUELLA IN THE CASE OF A CHILD WITH PERIOSTEAL POLYOSTEOPATHY. Q. SILVANO, Clin. pediat. **36**:571 (Aug.) 1954.

A prematurely born infant was admitted to the hospital at the age of 8 months for bronchitis; x-ray studies of the skeleton at this time revealed a quite generalized thickening of the periosteal shadows, which were quite distinct from the shadows of the bones themselves. The picture was quite similar to that described by Caffey and Silverman. The child recovered from his bronchitis. When seen two years later, the periosteal shadows were no longer apparent on x-ray, but the child had developed an oxycephaly.

HIGGINS, Boston.

MYOSITIS FIBROSA WITH CALCIFICATIONS CALCINOSIS UNIVERSALIS. JOSE OBES POLLERI, RENE MAGNOL, ALBERTO L. MATTEO, and N. TOLEDO, Arch. pediat. Uruguay **25**:583 (Sept.) 1954.

A case of myositis fibrosa with generalized soft-tissue calcification is reported. As usual, serum levels of calcium, phosphorus, and phosphatase were found to be within normal limits. A short trial with cortisone revealed no effect on subcutaneous nodules or range of motion of limbs. Modern concepts are reviewed.

FROM THE AUTHORS' SUMMARY.

Books

Clinical Management of Behavior Disorders in Children. By Harry Bakwin and Ruth Morris Bakwin. Price, $15. Pp. 495. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1950.

This is one of the major recent books which aims at increasing understanding of and developing skill in dealing with behavior or emotional problems of children. It contains a great deal of value. The sections on superior intelligence, special talent, mental defect, and pseudofeeblemindedness are excellent. The recent pertinent literature on the care of the physically ill, the handicapped, and the psychophysiological problems is well reviewed.

Three tools are necessary in attempting to treat or prevent behavior problems. The first and basic is the attitude of the physician. He needs to have a warm genuine objective interest in his patients and their parents. This book certainly encourages this point of view. Secondly, the physician needs some kind of reasonable well-organized broad understanding of the complex forces which shape personality development. This is necessary in order to understand the behavior of children and to influence it consciously toward healthy development. In this area the authors seem to be presenting a limited point of view. Symptoms are given undue prominence. Although the authors are clearly aware that behavior is only the crude outward sign of inner organization, their emphasis on symptomatic treatment tends to negate this fundamental fact.

The third essential is technical skill, which comes only from experience and most effectively from closely supervised experience. No book can substitute for this, however well it enriches understanding. A beginning is being made in offering this kind of training to the medical student and resident, but an effective means has not yet been devised of offering it to practicing physicians.

Study of the Visual Perception of Deaf Children. By Helmer R. Myklebust, Ed. D., and Milton Brutten, Ph.D. Price, not given. Pp. 126, with 12 illustrations. Acta Oto-Laryngologica, Väpnargatan 6, Stockholm, 1953.

The principal object of the investigators is implied in the title of this monograph. As pointed out in the introduction, educators are not uniformly aware that deaf children may have deficiencies in reasoning and abstraction, social competence, emotional maturity, vision, and motor control. A historical survey of the conception of the interrelationship of functions for the furtherance of the biological goals of the organism serves as a preface for the entire project.

As will be surmised from the foregoing remarks, the methods and approach figure exclusively in the field of psychology. Intelligence studies, etiological classification, and controlled experimentation are carefully established. The experimental techniques include visual survey tests, drawing tests, board patterns, tachistoscopic investigation, perseveration studies, pattern reproduction, etc.

Deaf children demonstrated a marked inferiority to hearing children in the accuracy with which certain patterns were reproduced and in the capacity for adequate shifting to accommodate changing conditions. The need for the development of educational techniques to overcome these deficiencies is stressed.

The authors conclude that a deficiency in abstraction seems to underlie the disturbed perceptual function of the deaf child, that perception cannot be considered apart from general mental functioning, and that the disruption of the normal growth of the faculties of abstraction hampers or precludes the capacity of the organism for coping perceptually with certain classes of stimuli.

This is an extremely valuable scholarly investigation which will doubtless strengthen the foundation of the newly developing science of audiology. Psychologists, educators of the handicapped, and interested otologists will profit from studying it carefully.

Practical Fluid Therapy in Pediatrics. By Fountaine S. Hill. Price, $6. Pp. 275. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1954.

Careful planning and organization have gone into the preparation of this volume. As a result, a great deal of information concerning the details and rationale of management in fluid and electrolyte imbalance is made readily accessible to the clinician. The first 94 pages of the volume

are devoted to succinct though clear explanations of basic physiologic principles. Included are essential definitions which constitute the language of physiologic chemistry and which must be understood before proper interpretation of laboratory data is possible. Reminiscent of the technique employed with such good effect in "Physiology of the Newborn," by C. A. Smith, each chapter ends with a summary and finally with a section called "Clinical Conclusions."

Following the first section of the text, dealing with fundamental principles, the 143 pages in Section II are devoted to discussion of each major type of fluid and electrolyte problem encountered in pediatrics. Practical guides and specific regimens are suggested. Although the latter will not gain universal acceptance in all instances, they certainly cannot be seriously criticized. The use of well-conceived illustrative case reports with accompanying comments is particularly instructive. Finally, in Section III, the techniques of venipuncture, intravenous infusion, and hypodermoclysis are described. Throughout the text, tables, charts, and photographic illustrations have been exceptionally well chosen.

If there is a general criticism of the volume it stems from the fact that fluid and electrolyte relationships in health and disease are too complex to be adequately interpreted in such an abbreviated manner. However, in the opinion of this reviewer, an admirable job has been done, and the resulting book as a practical, well-organized reference will be extremely useful to a great number of pediatricians.

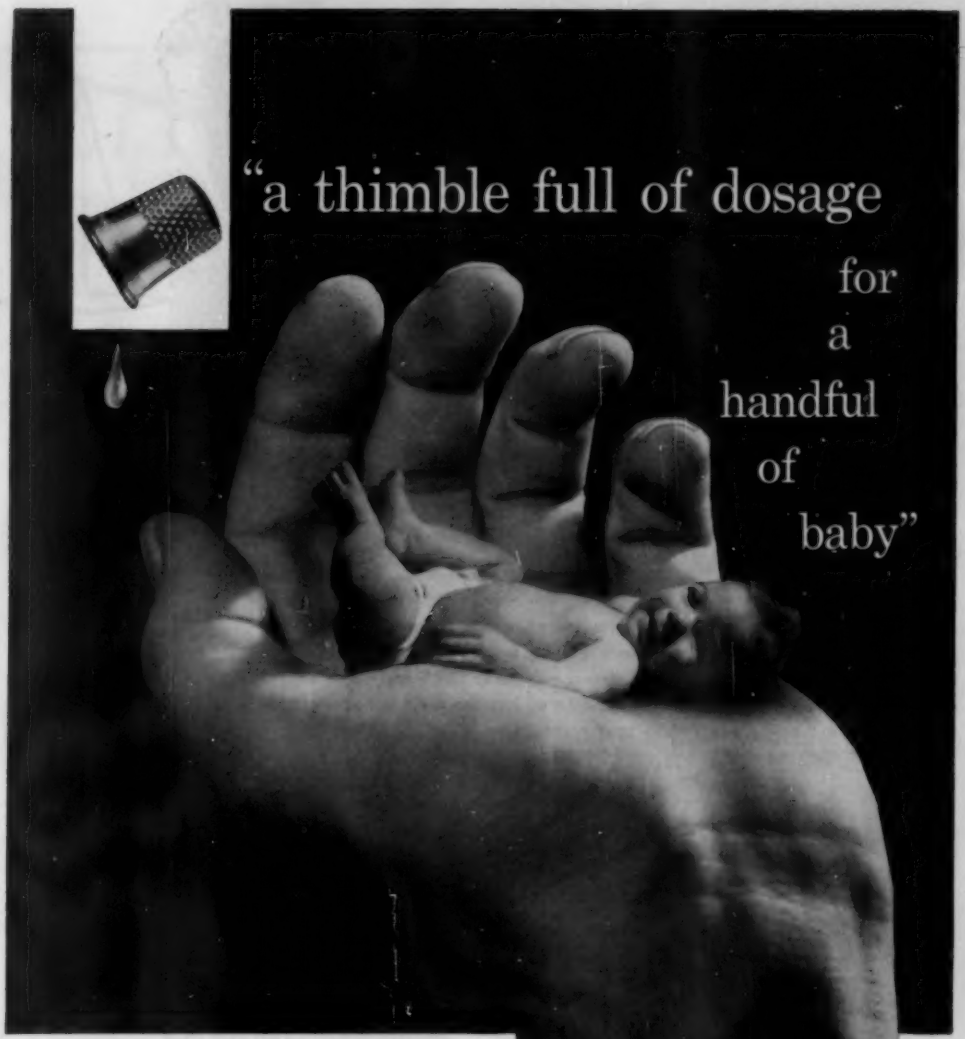
Emotions and Bodily Changes. Edition 4. By Flanders Dunbar. Price, $15. Pp. 1192. Columbia University Press, 2960 Broadway, New York 27, 1954.

This fourth edition of Dr. Dunbar's book is a monumental work which should be considered a classic in the field of psychosomatic medicine. Here in one volume is compiled a systematic survey of psychosomatic interrelationships. The book is outstanding as a reference work in that in addition to 751 pages of abstracted material there are 263 pages of bibliography.

The first part of the book consists of orientation and methodology, under which are discussed such subjects as "Problems of Integration and Differentiation," "Acute and Chronic Illness," and "Problems of Measurement."

Part 2 of the book is related to the great organ systems, so that one may review contributions pertinent to gastroenterology, cardiovascular medicine, endocrinology, etc.

In a volume of this size it is most difficult for a reviewer to cover the work in detail. Not being a psychiatrist, it would be presumptuous for this reviewer to attempt any specific criticism of the material presented. In general the information is interestingly written and stimulating reading. Despite the unquestionable importance of the psychosomatic phases of all branches of medicine, this is not a volume for daily use in clinical practice. It is, however, an outstanding reference work for those who wish to study in detail the various explanations and theories regarding psychosomatic interrelationships.



2.5 cc. Hypertussis eliminates massive dosage in whooping cough treatment or passive prevention. A crystal-clear homologous protein, 2.5 cc. Hypertussis contains the gamma globulin equivalent of 25 cc. of human hyper-immune serum. This specific anti-pertussis fraction is concentrated 10-fold to obviate the pain and inconvenience associated with massive dosage—giving you the advantage of

"a thimble full of dosage for a handful of baby."

Hypertussis will not interfere with the use of antibiotics where they may be indicated.

2.5 cc. Hypertussis is supplied in 2.5 cc. (one dose) vials, ready for immediate intramuscular injection.

CUTTER

CUTTER Laboratories
BERKELEY, CALIFORNIA

For whooping cough prophylaxis and treatment specify

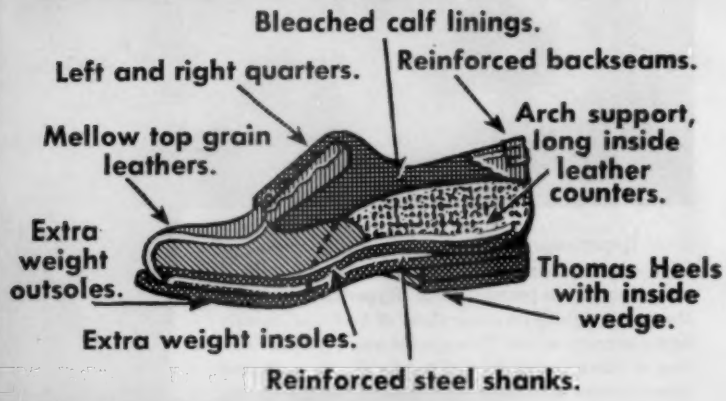
2.5cc. HYPERTUSSIS®

(anti-pertussis serum-human)

An Ounce of Prevention . . .

FLEET-AIR
ARCH LINE

Built to permit normal foot growth, Fleet-Air shoes feature custom built shanks and bulb shaped heel seats for adequate support and a firm, comfortable fit. In addition, soft porous uppers allow little feet to breathe . . . seamless linings eliminate any irritation from rough edges . . . flexible, sturdy soles permit bending at just the right point. Best of all, they are easily adapted to your prescription.



PARENTS of your little patients will be interested in our **FREE BOOKLET** titled, "The Proper Care of Your Child's Feet." In easy-to-understand language, it gives many important facts about the development of little feet. Send for your free copies today.

EBY SHOE CORPORATION

EPHRATA, PENNSYLVANIA

integrate your knowledge by reading these related specialty journals . . .

A. M. A. Archives of INDUSTRIAL HEALTH

A. M. A. Archives of INTERNAL MEDICINE

A. M. A. Archives of DERMATOLOGY

Designed to save you hours of reading time through visual presentations . . . to provide you with timely tips every month . . . to place useful information at your finger tips, leaving less information on your reference shelf.

Write for subscriptions to:
AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street
Chicago 10, Ill.
Dept. (PATH.)

a publication of the

World Health Organization

POLIOMYELITIS

With the current strides forward in the study of poliomyelitis the need for a volume such as this has become increasingly important. Here for the first time, brought together in one volume, is the work previously available only in many different publications. It contains comprehensive reviews of various aspects of poliomyelitis under five main headings:

- **Epidemiology**
- **Clinical Aspects**
- **Virology**
- **Immunology**
- **Control**

In the section on Virology Dr. John F. Enders, Nobel Prize winner, reviews the present status of tissue-culture techniques in the study of the poliomyelitis viruses, and in the section on Clinical Aspects the emergency management of respiratory and bulbar paralysis is described. 408 pp. Cloth, $8.00

INTERNATIONAL DOCUMENTS SERVICE

Columbia University Press
New York 27, N. Y.

A NEW SERIES IN

SEX EDUCATION

Titles in the new series

- PARENTS' PRIVILEGE
  for parents of young children of pre-school and early school age
- A STORY ABOUT YOU
  for children in grades 4, 5, and 6
- FINDING YOURSELF
  for boys and girls of approximately junior high school age
- LEARNING ABOUT LOVE
  for young people of both sexes (about 16 to 20 years of age)
- FACTS AREN'T ENOUGH
  for adults who have any responsibility for children or youth that may create a need for an understanding of sex education

PRICES

Note: Discounts apply to quantities of any single title, or to quantities of sets.

Quantity	Discount	Price
1	—	$ .50
10	10%	4.50
25	30%	8.75
50	40%	15.00
100	50%	25.00
1000	60%	200.00

Set of 5 titles, $2.25.

Distributed by

AMA SERVICES
Box No. 8610A
Chicago 77, Ill.

ORDER BLANK

Enclosed is $_____(no stamps) for the following pamphlet(s):

Title	Quantity
1. PARENTS' PRIVILEGE	_____
2. A STORY ABOUT YOU	_____
3. FINDING YOURSELF	_____
4. LEARNING ABOUT LOVE	_____
5. FACTS AREN'T ENOUGH	_____
Complete set of five	_____

Please send pamphlet(s) to:
(Please Print)

Name_____

Street_____

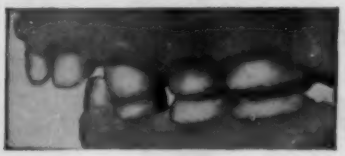
City_____

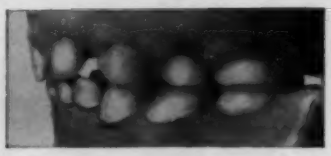
Zone_____ State_____

CD 9-55

THUMBSUCKING

since infancy caused this 4 year old's malocclusion.





THUM

TRADE MARK

THUM broke the habit and teeth returned to normal position in 9 months.

Get Thum at your druggist or surgical dealer. Prescribed by physicians for over 20 years.

PRESCRIPTION SERVICE FOR ALLERGIC DISEASES

Allergenic Extracts, Diagnostic and Therapeutic

Devoted exclusively to the manufacture of pollen, fungus, epidermal, food, dust, and miscellaneous allergenic extracts for the diagnosis and treatment of allergic conditions.

A pollen check list for your state and other literature sent on request.

U. S. Government License No. 103
since 1929

ALLERGY LABORATORIES, INC.

Pasteur Medical Building 1111 N. Lee Ave.
Oklahoma City 1, Oklahoma

AN APPROVED EDUCATION

FOR HOME - BOUND CHILDREN

Famous Calvert School-at-Home Courses for Kindergarten through 9th Grade

Physicians recognize the therapeutic value of the school routine for youthful patients. Many handicapped children show marked progress toward normal health when home-study courses are introduced. Thousands now get their elementary school education in their own homes with the famous Calvert *School-at-Home* Courses. Children afflicted by crippling orthopedic conditions, cerebral palsy, rheumatic fever, impaired hearing use the Calvert Courses on their doctor's recommendation. Calvert materials are complete in every detail—teaching manual, lessons, books and supplies. They are easily adapted to the child's mental, physical, emotional capabilities.

Calvert Courses are available for Kindergarten through 9th grade. They stimulate interest and curiosity. They permit children to advance at their own pace. More than 100,000 children have been taught by the Calvert method in the past 50 years. Calvert Courses are approved by the Maryland Department of Education.

Help parents of handicapped children solve difficult educational problems. Recommend Calvert *School-at-Home* Courses with confidence. Complete information sent promptly on request.

CALVERT SCHOOL

570 Tuscany Road Baltimore 10, Md.

YOUR
GUIDE TO
CURRENT PUBLICATIONS

Quarterly Cumulative Index Medicus

WITH AUTHORS AND SUBJECTS . . .

Divided into sections, one devoted to books and the other to periodical literature, the QUARTERLY CUMULATIVE INDEX MEDICUS contains a list of current publications alphabetized as to authors and subjects. The exact bibliographic reference is given under the author with titles in the original language, while titles under subjects are all in English. The index also includes a listing of journals, addresses and publishers.

The QUARTERLY CUMULATIVE INDEX MEDICUS appears twice a year; volumes are cloth bound and cover periodicals for six months as indicated on the publication. These two volumes will be a convenient and inclusive reference for current medical literature. Invaluable for practitioners, specialists, teachers, editors, writers, investigators, students and libraries.

SUBSCRIPTION PRICE $20.00 PER YEAR
CANADIAN AND FOREIGN $22.00 PER YEAR

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

For HARD, DRY STOOLS OF CONSTIPATED BABIES

Borcherdt

MALT SOUP *Extract**

A gentle laxative modifier of milk. One or two tablespoonfuls in the day's formula—or in water for breast fed babies—produce a marked change in the stool.

SAVES DOCTOR'S TIME, TOO!

Fewer phone calls from anxious mothers. Malt Soup Extract is merely added to the formula. Prompt results. Easy for mother to prepare and administer. Does not upset the baby.

*Specially processed non-diastatic malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

Send for Samples and Literature

BORCHERDT MALT EXTRACT CO.
217 N. Wolcott Ave. • Chicago 12, Ill.

Pioneers In the Manufacturing of Invalid Walkers — INVALEX — First In the Invalid and Sick Room Field

To Buy Invalex Sickroom and Invalid Equipment Produces a Satisfied User

GET UP — STAY UP

ADJUSTABLE FOR COMFORT

CLOSES TO 8 INCHES WIDE

Invalex Folding Walker
(2 Sizes - Jr. and Adult)
(3 Finishes)

GOES ANYWHERE

See Your Local Dealer or Write Us for Details

INVALEX **SALES CO., INC.**
741 W. Seventeenth St. Long Beach 13, California

Pancreatin

VIOKASE

NOT *enteric coated*

An accepted clinically effective* preparation in the treatment of disorders due to pancreatic insufficiency.

*Shwachman, H., Children's Hospital, Boston; The Child in Health and Disease, Gruleo and Eley, 2nd Edit.

Butler, A., Harvard Medical School, private communication.

Royce, S., Los Angeles Hospital, private communication.

Clay, W. A., Frank, D. W., and Logan, V. W., Studies on the Therapy of Pancreatic Insufficiency, Gastroenterology, 26: 169, 1954.

Everson, T. C., Grossman, M. I., and Ivy, A. C.: Bulletin of Amer. College of Surgeons, January, 1950.

Gibbs, G. E., Bradley, J. E., and Miner, J. V., Diagnosis and Treatment of Cystic Fibrosis of the Pancreas. J.A.M.A. 145: 1187 (1951).

Write for Literature

VioBin CORPORATION
MONTICELLO, ILLINOIS

because safety and nutritional effectiveness count so very much

specify **DEXTRI-MALTOSE**

MANUFACTURED SPECIFICALLY FOR INFANT FORMULAS

Dextri-Maltose is specifically designed for infant formulas—*and only infant formulas.* Unlike many milk modifiers, Dextri-Maltose is palatable but not sweet. It does not cloy the appetite. Infants fed Dextri-Maltose formulas do not develop a "sweet tooth" which may cause later resistance to essential foods.

The dextrins and maltose in Dextri-Maltose, plus the lactose of milk, give the infant a mixture of *three* different carbohydrates. These are broken down at different rates in the intestinal tract. Absorption is gradual. Sudden fluctuations in blood sugar levels are prevented.

Dextri-Maltose® is always kept safe and dependable through meticulous quality control. No other carbohydrate used in infant feeding has such a background of acceptance and dependability.

the importance of adequate added carbohydrate

Added carbohydrate provides calories needed to spare protein for tissue building, to permit proper fat metabolism and promote good water balance. Authorities on infant feeding recommend the addition of about 5% carbohydrate to milk and water mixtures. This proportion of carbohydrate is obtained by adding 1 tablespoon of Dextri-Maltose to each 5 or 6 ounces of fluid.

MEAD JOHNSON & COMPANY
EVANSVILLE, INDIANA, U.S.A.

MEAD

Meat...

and Biologic Facts of Protein Metabolism

The classical work of Cannon and his associates* in the field of protein metabolism has contributed significantly to our knowledge of the biologic utilization of protein. It has established that the dietary absence of a single amino acid quickly changes the direction of metabolic activity from anabolism to catabolism. Apparently all the nonessential amino acids play some part in sparing the essential amino acids, and all may be regarded as indispensable for optimal nutrition. It has been suggested "that for maximal tissue-utilization of amino acids at least twenty per cent of the total dietary nitrogen should come from other sources than essential amino acids."

In undernourished subjects the maintenance requirement for each essential amino acid is much greater—two to almost five times greater—than in healthy subjects.

Although an optimal caloric intake facilitates optimal utilization of amino acids, a reducing regimen need not curtail full utilization of these nutrients. It has been shown that a useful degree of amino acid utilization can be attained with caloric intake considerably below the optimal.

Minerals appear to be important in the process of amino acid metabolism. Evidence indicates that either phosphate or potassium deficiency might adversely influence amino acid utilization. Absence of either ion from experimental depletion rations leads to depression of appetite and slowing of the processes of protein repletion.

B complex vitamins also affect the metabolism of proteins and amino acids. For example, rats fed a high protein diet require a high intake of B complex vitamins in order to maintain normal growth rates. Omission from the ration of any one of these vitamins (riboflavin, thiamine, pyridoxine, or pantothenate) is accompanied, in varying degrees, by lower food consumption and slower weight gain.

Meat of all cuts and kinds is high in its content of protein, and provides well proportioned amounts of essential and nonessential amino acids. Meat also supplies valuable amounts of essential minerals, especially iron, phosphorus, potassium and magnesium, as well as important quantities of all components of the vitamin B complex, thus assuring maximal utilization of the amino acid components.

---

*Cannon, P. R.; Frazier, L. E., and Hughes, R. H.: Factors Influencing Amino Acid Utilization in Tissue Protein Synthesis, in Symposium on Protein Metabolism, New York, The National Vitamin Foundation, Inc., 1954, pp. 55-90.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute
Main Office, Chicago . . . Members Throughout the United States

ESSENTIAL TO PEDIATRIC NUTRITION

Cartose®

a mixed *liquid* carbohydrate

containing dextrose, maltose and dextrins. Each constituent has a different rate of assimilation, assuring spaced absorption, and preventing excessive fermentation, diarrhea and colic. Cartose is rapidly soluble in all milk formulas; does not form gummy, clogging particles. Supplied in bottles of one pint (1 tablespoon = 60 calories).

Drisdol®

is pure, synthetic vitamin D_3 (calciferol).

Drisdol in Propylene Glycol (tasteless, odorless, colorless and nonallergenic) disperses readily in milk, fruit juice, and other liquids — without floating or forming an adherent film — and mixes easily with solid food.
The average daily dose in milk of 2 drops for infants and from 4 to 6 drops for older children makes Drisdol highly economical. In bottles of 5 cc., 10 cc. and 50 cc., with special dropper (250 units of vitamin D per drop).

Also available:

Drisdol with Synthetic Vitamin A Dispersible

Each drop provides 1250 units of vitamin A and 250 units of vitamin D_2. No "fishy" taste or odor. In bottles of 10 cc. and 50 cc. with special dropper.

Winthrop-Stearns INC.
NEW YORK 18, N. Y. WINDSOR, ONT.

Cartose and Drisdol, trademarks reg. U. S. Pat. Off.